ABSTRACT

Title of Dissertation: REFINING THE PREDICTION OF RISK FOR SCHIZOPHRENIA: COMBINING PUTATIVE GENETIC AND NEURODEVELOPMENTAL MEASURES TO PREDICT SCHIZOPHRENIA-SPECTRUM PATHOLOGY

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Social anhedonia may be a promising indicator of an underlying genetic liability for schizophrenia. However, among socially anhedonic individuals, only a minority shows schizophrenia-spectrum disorders. In attempting to understand who may develop schizophrenia-spectrum disorders, researchers have hypothesized that schizophrenia may require both genetic risk and the presence of early environmental stressors (e.g., obstetric complications). "Developmental instability," which pertains to such early environmental stressors, refers to an organism's inability to buffer the effects of environmental insults on development, and has been associated with genetic risk for schizophrenia. Although one might expect developmental instability to also be elevated in individuals at psychometrically-determined risk for schizophrenia, this hypothesis has not been well-tested. This study examined two related questions using a cohort of psychometrically-identified high risk (socially anhedonic) and control 18-

year-olds, and their biological mothers: First, are measures of environmental insult (i.e., developmental instability and obstetric complications) higher in individuals at presumed genetic risk for schizophrenia-spectrum disorders (i.e., socially anhedonic individuals)? Second, do measures of environmental insult interact with putative genetic risk to predict poorer functioning on measures of clinical psychopathology and neurocognitive ability? Developmental instability was studied using fingerprints, minor physical anomalies and handedness. Obstetric history was obtained from biological mothers where possible. Results showed that socially anhedonic subjects had higher rates of one DI measure (minor physical anomalies) than controls. In addition, they were more clinically impaired in terms of mood disorders and schizophrenia-spectrum personality disorders, as well as overall functioning. Minor physical anomalies were also associated with higher ratings of schizophrenia-spectrum personality disorder symptoms within social anhedonics. Finally, there was an interaction between social anhedonia status and minor physical anomalies for Schizoid Personality Disorder symptoms, with the interaction associated with greater pathology over and above the contributions of each variable separately. These results support social anhedonia as an indicator of genetic liability for schizophrenia. Moreover, they suggest that developmental instability is associated with psychometrically-measured risk for schizophrenia, as well as with clinical pathology. The interaction between social anhedonia status and minor physical anomalies is in line with previous research demonstrating an interaction between genetic risk and environmental stressors.

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by

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Dissertation submitted to the Faculty of the Graduate School of the
University of Maryland, College Park in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
2004

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DEDICATION

I want to express profound gratitude to my mentor, Jack Blanchard, for consistent support and encouragement to integrate enthusiasm, life and values into work. I place great value on the critical thinking and skills I have learned in graduate school, and also on the ways in which I have been encouraged to find my voice as a researcher and clinician. I am so thankful to have worked with you.

ACKNOWLEDGEMENTS

I would like to thank my lab mates: Winnie Leung, Lindsay Collins, Kimberly Adams, Kari Tervo, Amy Buchanan and Kara Biondo, for help and support with this project, data, and life in general. I also want to thank Betty Padget for assistance with every step and detail of the graduate school process. Finally, I am very grateful to Hal Sigall for facilitating discourse and fairness in our educational climate; it has been a large source of support and energy to me in finishing my degree.

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CHAPTER 1: INTRODUCTION

Research approaching how to best predict which individuals will eventually go on to develop schizophrenia has taken several approaches. These include the examination of both genetic risk and early environmental stressors, such as obstetric complications, as well as predictors measured later in life, such as personality traits. The various risk factors have been successful in identifying groups of individuals with higher overall rates of schizophrenia-spectrum disorders (i.e., schizophrenia, Schizotypal personality disorder, Schizoid personality disorder, and Paranoid personality disorder) compared to the general population (e.g., Kwapil, 1998; Cannon, Mednick, Parnas & Schulsinger, 1994; Gottesman & Shields, 1972). To date, however, the problem of false positives remains: for example, among individuals psychometrically at risk, only a minority goes on to actually develop clinical disorders (Kwapil, 1998). Furthermore, many studies to date have focused exclusively on one domain of risk, such as obstetric complications or personality characteristics. Thus, a major aim of future research could be the integration of various risk factors, with the goal of increasing both prediction and understanding of the development of schizophrenia

It is possible that the issue of specificity of prediction might be addressed by combining markers of early developmental risk factors with psychometric measures of personality thought to identify genetic schizotypes. The utility of such an approach will be established through a discussion of the current understanding of risk for and development of schizophrenia. As such, various approaches to predicting and understanding schizophrenia-proneness will be discussed, including psychometric

high-risk paradigms, genetic models for schizophrenia, and neurodevelopmental theories of liability such as the developmental instability concept.

CHAPTER 2: PSYCHOMETRIC INDICATORS OF RISK FOR SCHIZOPHRENIA

Measures of Schizotypy

According to Meehl's definition of schizotypy (Meehl, 1962), there exists a latent class of individuals who have a specific genetic liability for schizophrenia. He termed this condition schizotaxia, and posited that it represented a necessary but not sufficient condition for the development of schizophrenia-spectrum disorders. He hypothesized that, through social learning and early experiences, all individuals with schizotaxia would develop a personality structure he termed "schizotypy". As conceptualized by Meehl (1962), schizotypy includes core features of anhedonia, as well as cognitive slippage, interpersonal aversiveness, and ambivalence.

The Revised Social Anhedonia Scale (RSAS; Eckblad, Chapman, Chapman & Mishlove, 1982) is a widely used paper and pencil measure developed to assess anhedonia as associated with schizotypy. The RSAS loads heavily on a "negative schizotypy" factor characterized by social avoidance. This focus on "negative schizotypy" distinguishes the RSAS from other measures of schizotypy such as the Magical Ideation Scale (MIS; Eckblad & Chapman, 1983) and the Perceptual Aberration Scale (PAS; Chapman, Chapman & Raulin, 1978), which load on a "positive schizotypy" factor (unusual beliefs and sensory/perceptual experiences). Although the MIS and the PAS are typically highly intercorrelated (Horan, Blanchard, Gangestad & Kwapil, manuscript under review), they are largely uncorrelated with the RSAS.

Cross-sectional Research

The concurrent validity of the three schizotypy measures (RSAS, MIS and PAS) has been examined in terms of three major areas: response patterns across family members; neurocognitive and physiological abnormalities; and clinical pathology and specific schizophrenia-spectrum liability. If the scales are actually tapping schizotypy, individuals identified as deviant through psychometric detection should manifest similar deficits and characteristics to those seen in individuals with schizophrenia. Comparisons of putative schizotypes with individuals with schizophrenia on these three variables will be reviewed below.

Response patterns in families: Response patterns in family members of a proband with schizophrenia have been examined in order to see whether psychometric deviance appears to coincide with known genetic risk. Research has shown that compared to controls, individuals with schizophrenia and those at known genetic risk (i.e., family members of probands) both show elevations on measures of perceptual aberration (PAS) and on a combined perceptual aberration/magical ideation scale (Berenbaum & McGrew, 1993; Lenzenweger & Loranger, 1989), as well as on measures of social anhedonia (RSAS; Blanchard, Mueser & Bellack, 1998; Chapman et al., 1976; Cook & Simukonda, 1981; Katsanis, Iacono & Beiser, 1990; Kendler, Thacker & Walsh, 1996). These findings support the scales as measures of schizotypy, and indicate that abnormal responding on the psychometric scales appears to coincide with genetic liability for schizophrenia.

Neurocognitive abnormalities in schizophrenia: The neurocognitive picture of schizophrenia is characterized by multiple impairments in functioning across a variety of neuropsychological domains. Research has shown that individuals with

schizophrenia have deficits in attention (e.g., Chen et al., 1998; Franke et al., 1994), working memory (Park & Holzman, 1992; 1993), executive functioning (Green et al., 1990) and oculomotor functioning (Crawford et al., 1998; Lencer et al., 1999). Such deficits are also present in family members with schizophrenia (e.g., Cannon et al., 1994; Faraone et al., 2000). These data indicate that neuropsychological dysfunction may be a useful phenotypic indicator of genetic schizotypy (Faraone et al., 2001).

In support of the conjecture that psychometric measures may accurately identify schizotypy, research has shown that psychometrically-identified schizotypes (according to measures of social anhedonia [RSAS], perceptual aberration [PAS] and magical ideation [MIS]) also appear to be deviant on measures of neuropsychological functioning. Across the three scales, individuals with high scores are reported to exhibit many of the same neuropsychological and psychophysiological abnormalities as those seen in patients with schizophrenia, including difficulties in sustained attention (Lenzenweger, Cornblatt & Putnick, 1991), working memory (Park, Holzman & Lenzenweger, 1995; Tallent & Gooding, 1999), eye-tracking (Gooding, 1999; O'Driscoll, Lenzenweger & Holzman, 1998) and executive functioning (Gooding et al., 1999; Kwapil & Tallent, 1999; Lenzenweger & Korfine, 1994; Park et al., 1995). The findings that psychometrically-identified schizotypes show the same pattern of neuropsychological impairment as seen in schizophrenia lends credence to the validity of these scales.

Clinical pathology and specific liability for schizophrenia-spectrum disorders: The various psychometric measures of schizotypy all show concurrent validity in terms of their convergence with familial response patterns and neuropsychological

markers of risk. However, in terms of their relation to psychological functioning and specific familial liability, the validity of the scales appears to differ. Evidence suggests that the Perceptual Aberration Scale (PAS) and Magical Ideation Scale (MIS) appear to tap broad family liability for a variety of psychotic disorders, including affective psychoses, but not schizophrenia (Chapman, Chapman & Kwapil, 1995; Chapman & Chapman, 1987; Katsanis, Iacono & Beiser, 1990). By contrast, the Revised Social Anhedonia Scale (RSAS) may identify specific liability for schizophrenia-spectrum disorders (e.g., Clementz, Grove, Katsanis & Iacono, 1991; Grove et al., 1991; Katsanis et al., 1990). In addition, social anhedonia as measured by the RSAS is associated with higher rates of Paranoid and Schizoid personality disorder features, while measures of perceptual aberration and magical ideation are not (Blanchard & Brown, 1999).

Taken as a whole, the data from response patterns in individuals at known genetic risk, neuropsychological performance and clinical pathology support all three scales as measures of psychosis-proneness. In terms of measuring specific liability for schizophrenia, however, the RSAS, which measures social anhedonia, appears to be a superior measure of schizotypy to the PAS and the MIS, which measure perceptual aberration and magical ideation. Nonetheless, this conclusion based on the data reviewed above is tempered somewhat by the nature of the research: due to its restriction to a single observational period, cross-sectional data cannot establish causal relationships between variables. In the case of validating social anhedonia as an indicator of genetic schizotypy, this is particularly important, as data shows that

transitory social anhedonia may be seen in other disorders, such as depression (Blanchard, Horan & Brown, 2001).

Prospective research

Compared to the cross-sectional studies reviewed above, prospective longitudinal studies are better able to address causal hypotheses relating to anhedonia. A 10-year follow-up study by Chapman et al. (1994) found that individuals with higher rates of perceptual aberration and magical ideation as measured by the PAS and MIS at baseline were at significantly higher risk for developing various psychotic disorders (both mood and non-mood) by the follow-up. However, neither scale was specifically predictive of schizophrenia-spectrum disorders in particular. By contrast, later analysis of the data demonstrated that high scores of social anhedonia on the RSAS (when scores on the PAS and MIS were controlled for) was associated with greatly elevated risk for development of schizophrenia-spectrum Axis 2 disorders; 24% of the socially anhedonic group developed such a disorder compared to 1% of the control group (Kwapil, 1998). Within the high MIS group, concurrently elevated RSAS scores also predicted higher rates of development of psychotic disorders (Chapman et al., 1994; Kwapil et al., 1997). When examined together, the cross-sectional and prospective studies of the MIS, PAS and RSAS further support the theory that all three scales identify individuals with higher genetic liability for psychosis. However, the RSAS appears to be a specific indicator for schizotypy, the genetic liability for schizophrenia-spectrum disorders in particular.

As reviewed above, social anhedonia has been shown to be the most promising indicator of schizophrenia-spectrum liability of the personality measures studied. However, the data suggest that it may be inadequate when used alone. The

limitation of social anhedonia as a stand-alone marker for risk lies in its imprecision: though socially anhedonic individuals show greatly elevated rates of schizophrenia-spectrum disorders (e.g., 24% vs. 1%; Kwapil, 1998), a substantial majority of social anhedonics do not go on to develop clinical pathology. This imprecision may be due to the inherent difficulty of using personality as a putative indicator of genetic risk; though schizotypy may be one pathway to social anhedonia, it is possible that many other unrelated factors (e.g., life events, social learning, depression) may also lead to an adult who is socially anhedonic (Blanchard et al., 2001). In light of the heterogeneous factors contributing to phenotypic expression, it has been suggested that neurodevelopmental markers such as ocular motor dysfunction or brain functioning may provide a more accurate means of identifying those at genetic risk, as they are closer to the endophenotype and measure aspects of early neurodevelopment (e.g., Faraone et al., 2001; Michie et al., 2000; Sponheim et al., 2001).

In order to evaluate this suggestion, it is first necessary to examine the current models of genetic risk themselves. Most importantly, the trajectory of neurodevelopment leading to schizophrenia-spectrum disorders (or not) given the genetic diathesis must be understood, as it provides evidence for the utility of various biological markers for understanding schizotypy. As such, the major models of genetic transmission will be reviewed, as will biological and environmental factors believed to contribute to the development of schizophrenia-spectrum disorders. This discussion will be used to justify the benefits of augmenting psychometric detection methods with more endophenotypic markers to detect true liability for schizophrenia.

CHAPTER 3: GENETIC MODELS OF SCHIZOPHRENIA

Multi-factorial Threshold Model

Among the major models proposed for the genetic liability of schizophrenia are the general single locus model (Meehl, 1989) and multifactorial threshold model (Gottesman & Shields, 1967). Meehl's general single locus model suggests that schizotaxia, a condition arising from a single gene, interacts with both pre- and post-natal developmental processes to give rise to phenotypic schizotypy and possibly schizophrenia. In individuals who escape clinical pathology, subtle signs of schizotypy (e.g., neurological soft signs, personality abnormalities) should still be present (Meehl, 1989). In contrast to this single gene theory, the multifactorial threshold model posits that multiple genetic factors are involved in schizophrenia liability, and that they act additively; in some individuals, the number of factors crosses a threshold, beyond which they result in the eventual development of schizophrenia. Under the multifactorial threshold model, environmental factors (e.g., birth complications, negative environments) may act either protectively or detrimentally, raising or lowering the threshold for phenotypic expression, and thus affecting the degree of risk for development of the disorder (Gottesman, Shields & Hanson, 1982).

Studies on incidence rates of schizophrenia-spectrum disorders within families reveal patterns more consistent with the multifactorial threshold model than Meehl's general single locus model (Yeo et al., 1999). Additionally, research has supported the role of early pre- or peri-natal stressors in affecting risk for development of schizophrenia (e.g., Cannon et al., 1993; Cannon, Mednick & Parnas, 1989; Mednick

et al, 1998). In light of their importance, these environmental factors have been integrated with genetic liability in the "2-hit" model of schizophrenia.

2-hit model

The "2-hit" model of the development of schizophrenia proposes that genes and pre- and peri-natal events act jointly to determine the eventual development of the disorder (Cannon et al., 1989). The 2-hit model is a diathesis-stress model, in which development of schizophrenia requires both the genetic liability and an environmental insult that serves to "push" structural changes in the brain involved in the disorder (Cannon et al., 1989). Support for this model comes from a variety of retrospective studies on rates of obstetric complications among individuals with schizophrenia.

Research on adult individuals with schizophrenia has shown significantly elevated rates of obstetric complications (e.g., hypoxia, maternal illness, low birth weight) compared with those seen in the general population (e.g., Goodman, 1988; Parnas et al., 1982). Furthermore, among the offspring of mothers with schizophrenia, there is evidence that those children with more perinatal birth complications were the ones who were most likely to develop schizophrenia (Parnas et al., 1982). It has been proposed that obstetric complications may interact with genetic liability rather than act as simple additive risk factors; that is, obstetric complications may only be pathogenic in the presence of the genetic diathesis for schizophrenia (Parnas & Mednick, 1990). This hypothesis is bolstered by evidence that the interaction of genetic risk with obstetric complications can be used to predict

developmental brain abnormalities seen in schizophrenia, such as enlarged ventricles (Cannon et al., 1993).

Limitations of Genetic Theories of Schizophrenia

Genetic theories of schizophrenia, while they can account for a significant portion of the disorder's development, have faltered on the immense heterogeneity within the disorder. Although presumably subject to the same etiological genetic processes, individuals with schizophrenia vary widely on clinical presentation, course, and outcome, as well as neurocognitive function and structural abnormalities (Markow, 1992) and brain asymmetry and lateralization patterns (Rosa et al., 2000). As noted in Yeo et al. (1999), if these abnormalities were caused by a single underlying genetic process, the various abnormalities should be highly intercorrelated. However, findings that both functional and structural asymmetries correlate either weakly or not at all argue against their being caused by a common gene or set of genes (Yeo et al., 1999). In addition, the failure of selection factors to reduce transmission of a disorder associated with severe impairment, decreased adaptive functioning and lowered fertility (Gottesman, 1991) are difficult to explain if only one genetic process is responsible (Yeo et al., 1999). One avenue that may offer a way to understand much of this heterogeneity in schizophrenia is the concept of developmental instability.

CHAPTER 4: DEVELOPMENTAL INSTABILITY

Introduction

A major issue in schizophrenia research has been determining a core etiological pathway for the inheritance and progression of the disorder. As discussed above, although research has demonstrated that liability for schizophrenia has a strong genetic component (e.g., Gottesman et al., 1982), the precise nature of inheritance remains unclear. In addition, many factors have been identified as risk factors for pathology, including pre- and peri-natal birth complications (Cannon et al., 1993) and environmental stressors later in life (Walker & Diforio, 1997). Developmental instability (DI) refers to an individual's inability to buffer the effects of environmental stressors on his or her development, and has been proposed as a core etiological pathway for the early brain developmental processes involved in schizophrenia (Yeo et al., 1999). Moreover, DI may provide a theoretical framework in which to integrate the impact of stressful environmental events across the life-span.

In order to evaluate the role of DI in schizophrenia, the concept will first be considered in light of current genetic theories of schizophrenia. Studies assessing markers of DI in schizophrenia will also be reviewed in order to establish whether DI is elevated among patients with schizophrenia, and whether it is related to clinical course. Finally, the role of DI in lifetime trajectory models of schizophrenia, including early development and environmental insults (e.g., obstetric complications), will be discussed.

Defining the Concept of Developmental Instability

The concept of DI has been proposed as a mechanism underlying much of the heterogeneity of schizophrenia (Yeo et al., 1999). The DI model is rooted in the assumption that the ability of an organism to precisely carry out its genetic "design" is an imprecise, epigenetic process. Increased developmental stability acts to "buffer" development, allowing the organism to express its genotype precisely even in the face of adverse environmental conditions (Waddington, 1957). Studies have supported developmental stability as an adaptive trait; across a variety of species, higher measurements of stability are associated with both longer life-span and more offspring (Yeo & Gangestad, 1998).

It is hypothesized that DI is related to homozygosity, both at the single loci-level and at the overall genomic level (Markow, 1992). In more heterozygous individuals, more than one form of a gene is present at any given locus, each with potentially different suitability for various environmental stressors; heterozygosity thereby increases fitness by increasing the individual's probability of being metabolically efficient in a variety of environments (Yeo et al., 1999). However, even two heterozygous individuals may produce a child with homozygous genes through random combination of genes during sexual mating, which may account for the continuation of DI in the population despite its relation to lower adaptation (Yeo et al., 1999; Markow, 1992). For continuous, multi-factorial polygenic traits (height, weight, etc), multiple genes act additively to determine location on the phenotypic continuum. Thus, increased heterozygosity tends to "average out" across genes, conferring phenotypes within the central part of the trait distribution. By contrast, more homozygosity across genes acts additively, resulting in extreme phenotypes at

the ends of the trait distribution. Phenotypic extremity can therefore be viewed as indicative of underlying polygenic homozygosity, and presumably therefore increased DI and decreased fitness (Markow, 1992).

Support for this hypothesis comes from a multitude of direct and indirect studies, both with humans and animals. For example, because birth weight in infants is a continuous and polygenic trait, extremely high or low birth weights can be assumed to reflect relative homozygosity and thus DI. Studies demonstrating that both low and high birth weights are associated with higher mortality support the inverse relationship between DI and fitness (Karn & Penrose, 1951, in Markow, 1992). Research measuring homozygosity directly has also supported its relationship to increased phenotypic extremity and DI. In rainbow trout, symmetry of pectoral fins is a continuous distribution around a symmetric population mean, and increased asymmetry has been associated with increased protein homozygosity (Leary et al., 1975, 1983, 1984, in Yeo, Gangestad & Daniel, 1993). Slow fetal growth rate, another marker of DI, has also been linked with protein homozygosity in a variety of species (see Yeo, Gangestad & Daniel, 1993).

Developmental Instability and Schizophrenia

If schizophrenia is conceptualized as a polygenic, multi-factorial threshold disorder (consistent with Gottesman's multifactorial threshold model), individuals who have the disorder must by definition possess sufficient numbers of the relevant genes to have crossed the threshold for expression. Their extreme phenotypic presentation may therefore be viewed as indicative of underlying polygenic homozygosity, which resulted in schizophrenia (Markow & Wandler, 1986). From a

DI perspective, this homozygosity should also be reflected in increased DI in individuals with schizophrenia.

While the concept of DI has been applied to schizophrenia, it is not unique to the disorder; studies have shown higher rates of DI in a wide range of neurodevelopmental disorders, including attention-deficit disorder, autism, cerebral palsy, and mental retardation (McGrath et al., 1995). Thus, schizophrenia may be conceptualized as resulting from two distinct genetic factors: those unique to schizophrenia and those related to DI and shared across other neurodevelopmental disorders (Yeo et al., 1999). With regard to the non-specific role of DI as a factor in schizophrenia, though it is not unique to schizophrenia, DI should nonetheless be seen in higher rates within the disorder as compared to the normal population.

Measuring Developmental Instability

Measurement of DI has typically relied on the identification of fluctuating asymmetry (FA), minor physical anomalies (MPAs) and directional asymmetries (DAs) as reflections of the organism's overall DI (Green, Bracha, Satz & Christenson, 1994).

Fluctuating asymmetries: Measurements of FA depend on the fact that certain traits, such as ear height or dermatoglyphic patterns, are bilaterally distributed such that they are symmetric at the genotypic and population level. However, individual phenotypic variation (imprecise development) creates a distribution around the mean, with individuals showing varying degrees of asymmetry in both directions. Since the genotype for these traits is perfectly symmetrical, the degree of departure from symmetry (FA) within individuals (e.g., the extent to which the ears are different

heights) is thought to reflect one's inability to precisely express one's genes, and thus one's degree of DI (Yeo & Gangestad, 1998).

Minor physical anomalies: The study of MPAs focuses on physical features particularly affected by fetal growth rate. Since different areas may have growth spurts at different points in fetal development, increased MPAs are thought to reflect abnormalities (slowing or disruption) at some point in fetal development (Yeo et al., 1999). For example, because the eyes migrate towards each other during the first trimester, interruptions of development by infections, toxins, or other environmental perturbations during the first trimester may result in the MPA of abnormally wide-spaced eyes (Green et al., 1989).

Directional asymmetries: Unlike FA and MPAs, DAs are naturally-occurring asymmetries where a certain degree of directional asymmetry is the norm (e.g., moderate right-handedness in humans; Markow, 1992), and deviation in either direction reflects phenotypic imprecision. Thus, both extreme right-handedness and mixed handedness/left-handedness would be classified as reflecting high DI (Yeo & Gangestad, 1998; Yeo et al., 1997).

Evidence for DI in Schizophrenia

Fluctuating asymmetry in schizophrenia: Studies of FA have demonstrated higher rates in patients with schizophrenia across a variety of measures. Patients with schizophrenia have been shown to have more dermatoglyphic asymmetries than control subjects on both quantitative measures (palmar and dermal ridge counts) and qualitative ones (dermal patterns) (Markow & Gottesman, 1989; Markow & Wandler, 1986; Mellor, 1992; Reilly et al., 2001; van Os et al., 1997). Comparisons of patients with schizophrenia to other psychiatric groups (e.g., affective disorder patients) have

also indicated that patients with schizophrenia have higher levels of dermatoglyphic asymmetries (Markow & Wandler, 1986). Studies measuring asymmetry of the ATD angle (the angles formed by the intersection of specific palmar lines) have also shown significantly more asymmetry in patients with schizophrenia as compared to normal controls (Mellor, 1992; Yeo et al., 1993; Yeo & Gangestad, 1998).

The AB ridge count at the base of the first and second fingers refers to the number of ridges touching a straight line between the a and b triradii (not including nascent ridges or triradial points) (Markow & Wandler, 1986); differences in number of AB ridges between right and left hands reflects the individual's DI. Among the various DI markers, the AB ridge count has been identified as particularly sensitive to environmental input because the area develops over an extended period of time relative to other dermatoglyphic traits (Fananas et al., 1996). Several studies have supported this conjecture, showing the AB ridge count to have the greatest levels of asymmetry among dermatoglyphic traits (Markow & Gottesman, 1989; Reilly et al., 2001). Researchers have suggested that the AB ridge count may thus be a trait marker for both developmental disturbances (Reilly et al., 2001) and liability for schizophrenia (Reilly & Gottesman, 1999).

A potential weakness of research on dermatoglyphics and schizophrenia is that several of the studies (e.g., Markow & Gottesman, 1989; Mellor, 1992; van Os et al., 1997) utilized archived data from studies originally carried out up to 50 years previously. Thus, diagnosis was based on chart reviews, and may not be accurate. Additionally, the latter two studies both utilized the Slater twin series (Slater, 1953, in van Os, 1997); it is unclear whether there was overlap in the subset of subjects each

study extracted from the larger group, and therefore whether the results from the two studies can be considered independent.

Minor physical anomalies in schizophrenia: Studies of MPAs, typically involving ratings made using variations of the Waldrop scale (McGrath et al., 1995), have shown elevated rates of MPAs in patients with schizophrenia (Buckley, 1998; Green et al., 1989; Guy et al., 1983; Lohr & Flynn, 1993; McGrath et al., 1995; Yeo & Gangestad, 1998). Although the literature provides support for an increased rate of MPAs in schizophrenia, however, the validity of the data is somewhat limited by the method of assessment. The Waldrop scale (Waldrop, 1975), is the most popular scale used in research on MPAs (Yeo, Gangestad & Daniel, 1993). Though relatively quick and easy to perform, the drawbacks of the scale are that it requires qualitative judgments (e.g., "fine, electric hair"), and, more importantly, lacks both normative data (particularly for different ethnic groups) and test-retest reliability (Buckley, 1998). Additionally, because the Waldrop Scale can be scored in a variety of ways, the presence or absence of group differences may depend on the scoring criteria used (Green et al., 1989).

There has been some suggestion that craniofacial and mouth abnormalities (e.g., high, steepled palate) may be especially elevated in patients with schizophrenia (Green et al., 1989; McGrath et al., 1995; Waddington et al., 1999). In light of these findings, and in response to the poor validity and reliability of the current assessment measures, researchers have proposed using morphometric strategies derived from surgery and anthropology to better study the relationship of craniofacial MPAs to schizophrenia in the future (Buckley, 1998).

Directional asymmetries (handedness) in schizophrenia: Research on directional asymmetries and DI in schizophrenia has largely focused on handedness. Evidence has suggested that rather than left-handedness or right-handedness being heritable per se, individuals seem to inherit a genetic tendency towards deviation from a universal genetic plan for moderate right-handedness (Yeo, Gangestad, Thoma, Shaw & Repa, 1997). Thus, deviations in either direction of the population mean are thought to reflect DI (Yeo, Gangestad & Daniel, 1993), as DI confers a susceptibility to non-directional deviation from the norm. In support of this hypothesis, studies have shown that both extreme right-handers and left-handers have more left-handed parents than moderate right-handers (Gangestad & Yeo, 1994).

A large number of studies have shown atypical handedness patterns in schizophrenia compared to normal populations (Cannon et al., 1995; Green et al., 1989; Nelson et al., 1993; Satz & Green, 1999), likely accounted for by an increase in ambiguous handedness (Reilly et al., 2001). Green and colleagues (1989) conducted a large-scale examination of multiple studies on ambiguous handedness, in which individuals show near-random choice of hand over a series of tasks. Based on the results of the meta-analysis, it was estimated that ambiguous handedness occurred in approximately 25% of schizophrenia patients (vs. 5% of normal controls).

It has been noted that the method of assessment may substantially alter designations of handedness: although 90% of the population is classified as right-handed based on self-report or observation of writing hand, only 65% are classified right-handed based on a multiple item questionnaire (Satz & Green, 1999). Studies have shown a relationship between the number of items on a handedness

questionnaire and the number of subjects classified as mixed-handed or left-handed (Satz & Green, 1999). Thus, it is often difficult to generalize rates of deviant handedness in schizophrenia across studies, as many researchers use different assessment measures.

Relationships between different measures of DI

Research on the relationship between FA and MPAs has generally shown them to be positively correlated (Green, Bracha, Satz & Christenson, 1994; Yeo, Gangestad & Daniel, 1993; Yeo et al., 1997). Handedness has also been shown to be related to other measures of DI. In two similar studies, Yeo, Gangestad & Daniel (1993) assessed the relationship between MPAs, FA (using the ATD angle and body measurements) and handedness (reported on a questionnaire and demonstrated on a peg-board task) in a sample of normal undergraduates. Results from both studies showed that MPAs and FA were significantly and strongly correlated with deviance from modal handedness ($r = .50$ and $.41$). Thus, both extreme right-handed and mixed- or left-handed subjects showed increased DI. In addition, self-reported handedness had a high (but not perfect) correlation with demonstrated hand performance ($r = .72$) (Yeo, Gangestad & Daniel, 1993). A third study on the relationship between handedness and DI by Yeo et al. (1999) replicated these results, with deviant performance on the handedness task being significantly correlated with DI. Although Yeo et al. (1993) had initially reported a U-shaped relationship between handedness and DI, the latter study more precisely described it as an inverted V-shape, with moderate right-hand dominance coinciding with the lowest DI (Yeo et al., 1999). Thus, the data suggest that any deviation from the norm of moderate right-handedness, regardless of direction, is associated with higher rates of DI.

Interestingly, different measures of MPAs and FA may be differentially suited for predicting handedness and cognitive lateralization. MPAs and dermatoglyphic FA are both formed very early in fetal development, likely near the end of the first trimester (Yeo et al., 1997). Similarly, hand preference has been demonstrated in thumb-sucking in fetuses at 18 weeks of gestation (Yeo et al., 1993). Handedness seems to be most related to MPAs and dermatoglyphics (see Yeo et al., 1993), and all three traits are likely the result of early developmental events. By contrast, cognitive asymmetries have been shown to be best predicted by body FA; unlike dermatoglyphics, which are formed early in fetal development, body FA may increase throughout the lifetime (Thornhill & Gangestad, 1994). It has been suggested that early environmental insults may thus have a greater relative effect on handedness, and result in dermatoglyphic FA, whereas later environmental insults may differentially affect body FA and cognitive lateralization (Yeo et al., 1997).

The Relationship of DI to Clinical Course of Schizophrenia

Findings of higher rates than normal of FA, MPAs and DA (handedness) abnormalities in schizophrenia samples support the hypothesis that schizophrenia is a disorder characterized by increased DI. However, the markers for DI (e.g., dermatologic and craniofacial abnormalities) are not in and of themselves detrimental. Rather, they are thought to reflect very early (1^{st} and 2^{nd} trimester) neurodevelopment gone awry. Although the DI markers are one end result of this disrupted development, many other clinical manifestations of schizophrenia are also thought to result from aberrant brain development. Thus, the DI model would predict that, within individuals with schizophrenia, those patients with increased levels of DI might have different clinical pictures than those with lower levels of DI. This issue

has been addressed in two main ways: by comparing groups of patients with schizophrenia with varying levels of DI on clinical variables, and by examining DI in monozygotic (MZ) twin pairs who are concordant or discordant for schizophrenia.

Studies of individuals: A study by Markow & Wandler (1986) demonstrated that increased DI (asymmetry of AB ridge count) was associated with earlier age of onset and higher ratings of long-term progressive deteriorating course of illness among patients with schizophrenia. Likewise, Green et al. (1989) found a relationship between MPAs and earlier age of onset in schizophrenia. A study of hand preference (assessed with a tapping task) in patients with schizophrenia showed that patients who showed more mixed-handedness were characterized by more pronounced psychotic symptoms and by worse response to medication (Gorynia & Uebelhack, 1992). Finally, one study has examined the relationship of psychometrically-determined schizotypy to DI. This study of adolescents with schizotypy as assessed by the Chapman scales (but no diagnosis of psychotic disorder) indicated that increased DI (AB ridge count) was associated with increased negative schizotypy (social and physical anhedonia), particularly in boys (Rosa et al., 2000).

Other studies of DI and clinical factors have had more equivocal or negative findings. McGrath et al. (1995) assessed the relationship of MPAs in psychotic patients with a variety of premorbid and current functioning variables, and found that higher rates of MPAs were associated with longer and more frequent hospital admissions, but not with the other variables (e.g., age of onset, negative symptoms, premorbid functioning, etc.). Three other studies (see McGrath et al., 1995) also failed to find an association between MPAs and age of onset in schizophrenia.

The overall results from studies of DI and outcome in schizophrenia, though somewhat variable, suggest that increased DI may be related to earlier age of onset and worsening course. Interestingly, results from a schizotypy sample suggest that the relationship of DI to schizophrenia-like personality traits (i.e., social anhedonia) may exist in individuals hypothesized to be genetic schizotypes even in the absence of full-blown schizophrenia. However, mixed findings from several studies support the need for further research on this topic. As noted by Tsuang, Stone & Faraone (2000), clinical symptoms are often non-specific, and may be the end results of multiple pathological processes. Thus, it is possible that clinical variables are too distal from the early fetal neurodevelopmental abnormalities indexed by DI markers to show reliable associations, particularly in smaller samples.

Twin studies: Twin studies on MZ twins discordant for schizophrenia allow researchers to address the difficulty of heterogeneity by using the well twin as the ill co-twin's control (Bracha et al., 1991). Since the twins are genetically identical, differences in clinical outcome can be more precisely examined in terms of their relationship to DI and environment, as any differences are presumably the result of a gene-by-environment interaction. Several studies have examined the relationship of DI to schizophrenia outcome in MZ twins. Bracha et al. (1991) found that for discordant MZ pairs, the ill co-twins had significantly more asymmetry and anomalies on measures of hand formation than the well co-twins. A second study also found greater dermatoglyphic asymmetry in ill MZ twins as compared to their well co-twins (Bracha et al., 1992).

Assessment of handedness in twin pairs discordant for both handedness and schizophrenia has shown that the ill twin is more likely to be the left-handed one

(Gottesman & Shields, 1972; Luchins, Pollin & Wyatt, 1980; Pollin & Stabeneau, 1968). The results of these studies support the conjecture that even though the twins have identical genetic liability for schizophrenia, the ill twins have experienced some non-shared environmental insult that has resulted in both disrupted fetal development (evidenced by atypical handedness) and the expression of their genetic liability for schizophrenia (Bracha et al., 1991). Findings of increased DI markers in the ill twins suggest that these events took place early in fetal development, as they disrupted processes known to take place during the first and second trimesters of fetal development.

If MZ twins concordant for schizophrenia are assumed to carry higher genetic liability than discordant pairs (Bogle, Reed & Rose, 1994; Gottesman & Shields, 1972), this increased genetic liability should be reflected in greater homozygosity, and consequently greater DI, in concordant versus discordant twin pairs (Yeo et al., 1999). This conjecture has been supported by several studies of concordant and discordant MZ twins. Markow & Wandler (1986) found that concordant MZ twins had significantly higher DI (AB ridge count) than discordant pairs, both in cases where the twin without schizophrenia was healthy and in cases where the twin without schizophrenia had another psychiatric illness. These findings were replicated by Markow & Gottesman (1989) using finger ridge count and pattern asymmetry; again, higher rates of DI were found in the concordant as compared to the discordant MZ twin pairs.

Two studies of handedness in MZ twin pairs have provided more refined theories with regard to DI and liability for schizophrenia. Boklage (1976; 1977) examined MZ twin pairs who were either both right-handed or had one or more twin

members who were non-right-handed. Replicating prior studies, he found elevated rates of atypical handedness among the twin pairs, particularly among pairs discordant for schizophrenia. In addition, non-right-handed individuals in twin pairs where either one or both of them were non-right-handed tended to score higher across measures of psychopathology (diagnosis, hospitalizations, global psychopathology ratings, unemployment) than their right-handed co-twins. However, when the concordance rates were compared between twin pairs, the twin pairs where one or both were non-right-handed had lower overall concordance rates for schizophrenia (25%) than did the pairs in which both were right-handed (92%). In addition, subjects with schizophrenia from the pairs in which both were right-handed had more serious forms of schizophrenia. These findings were replicated by Luchins, Pollin & Wyatt (1980). Unlike Boklage, however, the latter study found higher liability associated with individual non-right-handedness but equal rates of non-right-handedness among discordant and concordant twinships.

When results were pooled across these three studies, analyses showed that there was a higher risk for schizophrenia among non-right-handed twins compared to their right-handed cotwins (74% vs. 47%) in twinships in which one or both were non-right-handed (Luchins, Pollin & Wyatt, 1980). These findings are consistent with a DI model, suggesting that although the twins share genetic risk, the ill co-twin suffered an early neurodevelopmental insult resulting in both atypical handedness and schizophrenia.

The second part of these findings was that when schizophrenia did occur in twinships where both were right-handed, it seemed to take on a more severe, classic form, particularly in pairs concordant for the illness. These findings are somewhat

surprising given both predictions of greater homozygosity (and thus higher DI in concordant twin pairs based on DI theories; Yeo et al., 1999), and findings of greater DI in concordant versus discordant twins (e.g., Markow & Wandler, 1986; Markow & Gottesman, 1989). Notwithstanding, the findings may be understood under the multi-factorial threshold model of schizophrenia proposed by Gottesman, in which environmental factors (fetal abnormalities, obstetric complications) may serve to lower the genetic threshold necessary for expression of schizophrenia. In individuals with no evidence for early fetal stressors in the form of handedness abnormalities, etc., expression of schizophrenia may suggest a genetic component so substantial as not to require any lowering of the threshold via environmental stressors. Thus, right-handed twins with schizophrenia may represent a subset of individuals with a particularly virulent form of the illness, reflected in greater concordance rates with their co-twins, whereas non-right-handed twins with schizophrenia may represent individuals whose genetic liability was only potentiated through a (potentially non-shared) early stressor that also resulted in atypical handedness.

Conclusions: DI and Schizophrenia

A substantial body of research across a variety of developmental measures has demonstrated an elevated rate of DI in patients with schizophrenia. Within patients with schizophrenia, there is suggestion that increased DI may be related to more severe clinical course (e.g., earlier onset, worse prognosis). In addition, evidence from twin studies indicates that DI may differentiate the ill twin in discordant MZ pairs, supporting the hypothesis that the discordance may be due to an early, non-shared environmental insult. The importance of early environmental insults and aberrant neurodevelopment in schizophrenia is generally widely agreed-upon.

However, the DI perspective offers a unique theoretical framework in which to conceptualize multiple factors in a neurodevelopmental theory of the disease, as DI provides evidence for two related but separate phenomena: the presence of DI markers is proof not only of a history of developmental insults such as perinatal complications, but also of a heightened susceptibility to the effects of those early events. Neurodevelopmental theories of schizophrenia offer a means to understand the ways in which the DI literature contributes to our understanding of the developmental trajectory of schizophrenia.

CHAPTER 5: NEURODEVELOPMENTAL THEORIES OF SCHIZOPHRENIA

Obstetric Complications

Schizophrenia has been conceptualized using a diathesis-stress model, in which neurodevelopmental events interact with genetic liability to produce expression of the disorder (Waddington et al., 1999). Considerable evidence has accumulated to show that early environmental stressors, such as obstetric complications, may play a role in determining eventual development of full-blown schizophrenia. Patients with schizophrenia are more likely than normal individuals to have experienced fetal or obstetric complications (Geddes & Laurie, 1995; Goodman, 1988). Among children of mothers with schizophrenia, children with perinatal birth complications went on to develop schizophrenia more often than did the high risk children with uncomplicated births (Parnas et al., 1982). Within patients with schizophrenia, obstetric complications have also been related to structural brain deficits such as higher ventricle-to-brain ratios or widening of cortical sulci and fissures (O'Callaghan, Larkin & Waddington, 1995; Owen, Lewis & Murray, 1988), possibly through an interaction with genetic liability for schizophrenia (Cannon et al., 1989).

Though compelling, much of the research on obstetric complications is performed with retrospective research (e.g., Heun & Maier, 1993), which raises questions about the validity of maternal recall. However, comparison of maternal recall of obstetric complications with medical records of the births has suggested that maternal recall may be an accurate source of information (O'Callaghan et al., 1990). Moreover, prospective studies (Parnas et al., 1982) or those utilizing medical records (e.g., Cannon, Mednick & Parnas, 1989) have generally found the same pattern of

results as retrospective maternal recall studies. Thus, the research offers strong support for the role of obstetric complications in the risk and development of schizophrenia, indicating that they occur in a sizable minority (e.g., approximately 21-40%) of patients with schizophrenia (Buckley, 1998).

While some researchers consider obstetric complications to be a non-specific etiological factor in schizophrenia (Gottesman, Shields & Hanson, 1982), others believe that obstetric complications may be differentially important depending on genetic liability. That is, obstetric complications may confer risk for difficulties such as ventricular enlargement only in the presence of genetic liability (Cannon et al., 1993).

These findings can be fit into a DI model on two levels. First, the suggestion that obstetric complications may have differential effects depending on liability for schizophrenia may reflect the increased DI in those genetically liable individuals. Given that increased DI leads to poor ability to buffer the effects of the environment (as evidenced by minor errors in early development such as FA, MPAs, etc.), it is possible that obstetric complications have a particularly significant effect on genetic schizotypes due to their poor ability to buffer environmental stressors. From this perspective, the findings of an interaction between the effect of obstetric complications and genetic liability on schizophrenia reported by Cannon et al. (1993) could reflect the fact that in less genetically liable individuals, the fetal insult may have had fewer neurodevelopmental consequences than for the genetic schizotypes.

The second level of the relationship between DI and obstetric complications lies in causal interactions. Both obstetric complications and markers of early neurodevelopmental errors (evidenced by DI markers) have been found in individuals

with schizophrenia. However, as noted by Waddington et al. (1999), considering these two factors as separate, additional sources of developmental insult may lack parsimony. Given that the neurodevelopmental processes in schizophrenia (and markers for DI) reflect pathology that likely takes place during the first and second trimesters of fetal development (Waddington et al., 1999), it is not possible to consider obstetric complications, which come later temporally, as causal factors in this neuropathology. Rather, they may at least partially reflect unspecified insults or processes that have already caused disturbances early in fetal development (evident in FA, MPAs, etc), and later play a role in causing obstetric complications (Waddington et al., 1998).

Direct support for this relationship of DI to obstetric complications comes from a variety of studies relating both early and late fetal complications to congenital abnormalities indicative of early environmental insults (and DI). For example, low birth weight, which has been related to increased risk for schizophrenia, is also associated with reduced fetal growth in the first trimester (Smith et al., 1998). Thus, the DI perspective in a multifactorial threshold model might account for a process in which the genetic liability for schizophrenia results in increased DI, which in turn lowers the individual's ability to buffer early environmental insults. These events may lead to a neurologically-compromised fetus that is more likely to have obstetric complications, which then may interact with low buffering ability to possibly worsen impairments, and further increase risk for the expression of schizophrenia.

CONCLUSIONS

The identification of risk factors for schizophrenia has taken a variety of approaches. The psychometric high-risk paradigm, including measurement of social

anhedonia, uses personality as a putative marker for genetic schizotypy. Social anhedonia has been shown to predict specific liability for schizophrenia-spectrum disorders in both cross-sectional and prospective studies. Nonetheless, among social anhedonics, only a minority goes on to develop clinical pathology. Genetic models have met with similar problems in prediction, as well as the difficulty of explaining how a disorder associated with greatly lowered rates of reproduction has remained in the population. The concept of DI as a non-specific risk factor that may interact with other factors to produce the eventual development of schizophrenia is a compelling one. However, a greater understanding of how these various areas of research fit together is clearly needed. The integration of early developmental pathways (e.g., genetic, DI, pre- and peri-natal complications) with measures of later development (e.g., psychometric assessment of personality risk factors) might lead to a better understanding of the development of schizophrenia. Moreover, such an integration may lead to greater success in predicting which individuals among those thought to be high-risk will actually go on to develop clinical pathology.

CHAPTER 6: RATIONALE FOR CURRENT STUDY

To date, psychometric approaches to schizophrenia-spectrum liability have been relatively independent from genetic and neurodevelopmental theories. For example, the vast majority of the literature has focused on examining DI and obstetric complications in individuals who already have schizophrenia, or their immediate family members. Thus, it is not clear whether individuals identified as psychometrically high-risk on the basis of social anhedonia scores show increased rates of obstetric complications and DI markers as do patients with schizophrenia and those at known genetic risk. This question may be important for the understanding of how putative genetic risk is related to variables such as DI when genetic risk is assessed without regard for current symptomatology (as opposed to merely in those individuals who are currently ill with schizophrenia, or who are from families with a known history of schizophrenia).

As noted earlier, schizophrenia is a disorder with immense phenotypic (and potentially developmental) heterogeneity (e.g., Markow, 1992; Rosa et al., 2000), which may cloud the identification of individual risk markers or neurodevelopmental processes. It has been suggested that incorporating biological and brain indices closer to the endophenotype may improve sensitivity to latent genetic liability (Michie et al., 2000). The use of neurodevelopmental markers such as obstetric complications and DI in combination with psychometric paradigms to identify individuals within a group of putative schizotypes would be one such application. In light of literature suggesting that social anhedonia is a promising indicator of schizotypy, one would expect that schizotypes identified using the RSAS should show similar patterns of

obstetric complications and DI as do individuals at known genetic risk for schizophrenia. Based on the suggestion that endophenotypic markers may be more sensitive than clinical phenotypic ones, it is possible that elevations on measures of obstetric complications and DI within the social anhedonia group would more accurately identify those at highest risk for schizophrenia-spectrum pathology. To date, however, these hypotheses have not been tested.

CHAPTER 7: STUDY HYPOTHESES

This study used a community sample of 18-year olds to identify both socially anhedonic and non-socially anhedonic individuals. These subjects were assessed in the lab with a variety of clinical and neuropsychological measures. In addition, measurements of DI were made and subjects' histories of obstetric complications were obtained. The goal of the study was to identify a subgroup of psychometrically at-risk individuals at particularly high risk of developing schizophrenia-spectrum pathology due to a combination of both genetic and environmental vulnerability. The data were used to address a number of hypotheses:

1. As conjectured by Meehl (1962), social anhedonia may be a putative indicator of schizotypy. A history of obstetric complications and the presence of DI markers can be construed as evidence both of early environmental insults and of developmental instability. Based on prior literature, it was expected that there would be greater rates of DI markers (as measured by handedness, minor physical anomalies, and fluctuating asymmetries) and obstetric complications among the socially anhedonic subjects compared to control subjects.
2. It was expected that DI and obstetric complications, as well as social anhedonia, would be associated with greater psychopathology on a variety of clinical measures (Axis I and II, Global Assessment of Functioning [GAF] scores). Due to the young age of the subjects (i.e., 18), it was expected that few of them would yet show frank psychosis, but would rather tend to show elevations on schizophrenia-spectrum personality disorder symptoms, and

poorer global functioning as measured by the GAF. Based on evidence that genetic risk and early developmental insults may interact rather than simply act additively in schizophrenia (Cannon et al., 1993), it was predicted that there would be both main effects and a positive interaction on the various clinical measures.

3. It was hypothesized that DI and obstetric complications, as well as social anhedonia would also be associated with greater impairment on neuropsychological measures of attention, working memory and executive functioning, in the same pattern as that seen in patients with schizophrenia. Both main effects and a positive interaction were expected.

CHAPTER 8: METHODOLOGY

Subjects for the current study were recruited as part of a NIMH grant-funded five-year longitudinal study entitled "Social Anhedonia and Schizophrenia-Proneness" being conducted by Dr. Jack Blanchard at the University of Maryland, College Park (UMCP). That study received original approval from the UMCP Institutional Review Board (IRB) in February, 2001, and was reapproved in August, 2001. The current study received IRB approval in May, 2002 (see Appendix A), and involved the administration of additional measures of neurodevelopmental risk not included in the grant study.

Subjects:

Subjects for the grant study were recruited by the UMCP Survey Research Center (SRC) by using random-digit dial methods to identify households within a 15-mile radius of the UMCP campus in which there was an 18-year old. For those subjects who consented, a consent form and questionnaire was mailed to them. The questionnaire contained the Revised Social Anhedonia Scale (RSAS), the Magical Ideation Scale (MIS) and the Perceptual Aberration Scale (PAS), as well as an infrequency scale (IS; Chapman et al., 1976) used to exclude invalid responders. A total of 1284 respondents returned surveys. Of these respondents, 45% were male and 55% were female. The sample was racially diverse, with 45.1% being White, 31.0% being African-American, 9.7% being Asian and 12.9% being "other". Less than 1% of subjects refused to give their race. Because of concerns that there might be a bias in RSAS scores due to race or sex, the RSAS scores were z-scored

separately by race and sex. For each group, socially anhedonic subjects were selected on the basis of having RSAS scores of 1.8 or more standard deviations above the mean, while control subjects were selected to have RSAS scores of no more than 0.5 standard deviations above the mean. The control subjects also needed to meet the selection requirement of having low MIS scores (e.g., no more than 0.5 SDs above the mean on the MIS) to be considered. For all subjects, any questionnaires with invalid profiles based on the IS (e.g., more than 2 atypical responses; Chapman et al., 1976) were excluded. These selection criteria have been used in other, similar studies of social anhedonia and schizophrenia (e.g., Kwapil, 1998).

Control and socially anhedonic subjects were recruited from these groups for the second phase of the grant study through telephone calls and letters. Subjects who agreed to participate in this phase came to UMCP for a series of diagnostic interviews and neuropsychological tests, which typically took between 2.5 and 5 hours. In addition, the biological parents of participants were invited to complete the same procedures. All subjects were compensated $100 for their involvement. The present study asked 18-year old participants and their biological mothers at the time of their appointments whether they would like to complete additional measures (taking approximately 10-30 minutes) for an additional $15.

Measures: Screening (see Appendix B)

Revised Social Anhedonia Scale (RSAS): The RSAS is a 40 item True/False questionnaire. Concurrent validity of the RSAS has been demonstrated through findings that high RSAS scores are related to interview-based ratings of current social withdrawal and loneliness, as well as self-reported dimunition of need for and enjoyment of social interaction (Mishlove & Chapman, 1985). Items include

"although I know I should have affection for certain people, I don't really feel it" (keyed true); "When things are going really good for my close friends, it makes me feel good too" (keyed false) (Mishlove & Chapman, 1985). The RSAS has high test-retest reliability (Blanchard et al., 1998), and has been shown to be internally consistent (Blanchard et al., 1998; Mishlove & Chapman, 1985). As reviewed above, patients with schizophrenia and those at known genetic risk show elevated RSAS scores, and the scale has been shown to predict neuropsychological impairment and schizophrenia-spectrum disorders both cross-sectionally and prospectively.

Infrequency Scale: The IS (Chapman et al., 1976) is a 17 item scale consisting of items that are almost invariably answered in one direction (e.g., "there have been a number of occasions when people I know have said hello to me"; "I find that I often walk with a limp, which is the result of a sky-diving accident" etc.). Profiles with more than 2 abnormal responses were excluded. This approach has been used in other similar studies (e.g., Chapman et al., 1976; Blanchard et al., 2000).

Measures: Clinical

Diagnostic interviews: Participants were assessed for Axis I pathology using the mood, psychosis and substance use sections of the Structured Clinical Interview for the DSM-IV Axis I Disorders, Patient Edition- Research Version (SCID; First, Gibbon, Spitzer & Williams, 1996). This is a widely used semi-structured interview that has been shown to have good inter-rater agreement (e.g., kappas greater than .6; Williams et al., 1992), and has been used in other, similar studies of psychosis-proneness (e.g., Chapman et al., 1994; Gooding & Tallent, 2001).

The presence of schizophrenia-spectrum personality disorders was assessed on both a categorical and a dimensional level using the Schizoid, Schizotypal and

Paranoid sections of the International Personality Disorders Examination (IPDE: Loranger et al., 1995). Inter-rater reliability for dimensional scores has been shown to be high, ranging from .79 to .94 for the DSM-III-R (Loranger et al., 1994). This measure has been used to assess schizophrenia-spectrum pathology in other studies of psychosis-proneness (e.g., Blanchard & Brown, 1999; Brown, Blanchard & Horan, 1998; Chapman et al., 1994).

Global functioning: The Global Assessment of Functioning Scale (GAF; APA, 1994) was used to rate participants overall level of functioning. The GAF scale is a widely used standardized scale with a range of 1 (severe, life-threatening pathology) to 100 (superior functioning). It has been used in other studies of psychosis-proneness (e.g., Chapman et al., 1994), and has been shown to be superior to other measures at assessing adaptive functioning (Goldman et al., 1992).

Measures: Neuropsychological

Sustained attention: The Continuous Performance Test, Degraded Stimuli (CPT-DS; Nuechterlein et al., 1986) was used to measure sustained attention. This task involves discriminating highly blurred zeros from other numbers during an 8 minute trial in which the numbers are presented very briefly (40 milliseconds), one number presentation per second. The index of discriminability/sensitivity (d') on the CPT-DS has been widely used to measure sustained attention in schizophrenia (e.g., Cornblatt & Keilp, 1994; Nuechterlein et al., 1986), and also identifies impaired attention in relatives of patients with schizophrenia (e.g., Cannon et al., 1994; Grove et al., 1991).

Working memory: Three subtests from the Wechsler Memory Scale-III (WMS-III) were used to assess working memory: Digit Span (forward and

backward); Spatial Span (forward and backward); and Letter-Number Sequencing. These tests have been shown to have good stability and reliability for this age group (Psychological Corporation, 1997). The Digit Span and Letter-Number Sequencing tasks are designed to measure auditory working memory, while the Spatial Span task is designed to measure visuospatial working memory (Gold et al., 1997; Park & Holzman, 1992).

General memory: Although general memory deficits in both verbal and nonverbal memory have been observed in schizophrenia (Blanchard & Neale, 1994; Saykin et al., 1991), such deficits have not been examined in socially anhedonic individuals. The Logical Memory I and II and Visual Reproduction I and II subtests of the WMS-III were used to assess short and long term verbal and nonverbal memory, respectively. Stability and reliability for this age group on these tests has been shown to be good (Psychological Corporation, 1997).

General intelligence: Two subtests from the Wechsler Adult Intelligence Scale-III (WAIS-III; Wechsler, 1997) were administered to obtain an estimate of general intelligence. The two tests, Vocabulary and Block Design, have been shown to have good reliability; additionally, they have been shown to correlate highly with Full Scale IQ scores using the previous version of the WAIS, the WAIS-R (r=.90; Silverstein, 1982). This use of an abbreviated two-subtest estimate of general intelligence has been used in similar research (Gooding, Kwapil & Tallent, 1999; Keefe et al., 1994).

Measures: Developmental Instability and Obstetric Complications

Obstetric complications: A variety of retrospective self-report scales have been used to evaluate a history of obstetric complications. Research comparing such

retrospective reports to medical records suggests that retrospective research yields valid data (O'Callaghan, Larkin & Waddington, 1990). This study used a 15 item scale that represents a consensus of six such popular scales (Owen et al., 1988; see Appendix C for questions). The items tap complications from the antepartum period (e.g., pre-eclampsia), the intrapartum period (e.g., breech birth), and the post-partum period (e.g., incubation). Complications were rated as either definite or equivocal based on criteria for each item. For example, the item of "low birthweight" would be rated as definite in the case of a birthweight of less than 4.5 lbs, and equivocal in the case of 4.5 –5.5 lbs. Information on obstetric complications was obtained through face-to-face interviews with the mothers where possible, over the phone, or through the mail. Where there was uncertainty about an item, consensus ratings were made.

Directional asymmetry (handedness): A measure of relative hand skill was obtained using the Annett Peg-moving Task. This is a task of speed that involves moving pegs from one set of holes to another using first the right hand, then the left hand, for a total of 5 trials per hand. Directional asymmetry was calculated by comparing the relative performance of right and left hands. This task has been widely used in other studies of handedness (e.g., Gangestad & Yeo, 1994; Yeo, Gangestad & Daniel, 1993). Atypical handedness is related to other measures of neurodevelopment (Yeo, Gangestad & Daniel, 1993), and has been shown to differentiate individuals with schizophrenia and those at known genetic risk from the general population (e.g., Cannon et al., 1995; Green et al., 1989). In patients with schizophrenia, handedness has been associated with clinical measures, including symptoms and response to medication (Gorynia & Uebelhack, 1992).

Fluctuating asymmetries: As discussed previously, DI can be manifested as various asymmetries in traits that are genetically programmed to be symmetrical (e.g., finger and palm prints). In this study, fingerprints and palm prints for both right and left hands were obtained using standard inking procedures. Ratings were made of the AB ridge count (number of ridges between the triradius a, at the base of the index finger, and the triradius b, at the base of the middle finger; Holt, 1968), and the discrepancy between right and left hands was computed (Jantz & Webb, 1980). In addition, calculations were made of the ATD angle (the angle formed by lines connecting the triradius a and the triradius d, under the little finger, with a point t, on the lower outer portion of the palm, approximately under the fourth finger; Penrose, 1954), and the discrepancy between right and left hands computed (Yeo, Gangestad & Daniel, 1993). Finally, fingerprints were classified as loops, arches or whorls and the symmetry of pairs of fingerprints was compared. These procedures have been used in other, similar studies of FA (e.g., Markow & Wandler, 1986; Mellor, 1992; Rosa et al., 2000; Yeo, Gangestad & Daniel, 1993). Results from such studies have shown a relationship between FA and schizophrenia (e.g., Mellor, 1992; Yeo et al., 1993). In addition, within schizophrenia, FA is associated with age of onset and clinical course (Green et al., 1989; Markow & Wandler, 1986).

Minor physical anomalies: Minor physical anomalies (MPAs) were assessed using the Manual for Assessing Minor Physical Anomalies (Waldrop, Halverson & Shetterley, 1989; see Appendix D), which sets forth guidelines for determining the presence and degree of a variety of MPAs. These include wide-spaced eyes, low-seated ears, single transverse palmer crease, and anomalies of the fingers and toes.

This manual is the most popular assessment tool for MPAs (Yeo, Gangestad & Daniel, 1993). It has been used in many other studies of MPAs, including both those of individuals at genetic risk for schizophrenia, for whom it may be associated with clinical history and outcome (e.g., Shiffman et al., 2002), and those of normal college-age individuals (e.g., Yeo et al., 1997). MPAs as measured by Waldrop and colleagues' manual have been shown to remain stable from birth (Waldrop, 1975). Inter-rater reliability for the overall MPA score has been found to be high (e.g., .70; Waldrop, Pederson & Bell, 1968). Extensive norming has shown that the rate of MPAs in the general population is low (between 0-4), and high scorers (those with five or more MPAs) have been robustly associated with a variety of types of pathology (Waldrop, 1975).

Training

Clinical and neurocognitive measures: This study was conducted as part of a larger, ongoing grant-funded study by Dr. Jack Blanchard. All diagnostic interviews (SCID, IPDE) and neuropsychological testing (WMS-III, WAIS-III, CPT-DS) were conducted by trained graduate students supervised by Dr. Blanchard. Ongoing supervision was provided by Dr. Blanchard, and consensus ratings were used when there was doubt about an item.

Waldrop scale: Raters were graduate students trained using the Waldrop Manual. Discussion of the scoring criteria and group ratings on practice subjects were carried out prior to rating actual subjects in order to ensure agreement about the criteria. In addition, regular discussions about any difficulties in ratings took place during supervision, and periodic checks were conducted in order to ensure ongoing agreement.

Annett Peg-Moving Task: Evaluators were graduate students trained in the administration of neuropsychological tests. Subjects listened aloud as the evaluator read them scripted directions in order to keep the administration standard. Evaluators used an electronic stopwatch to begin and stop timing the subject at clearly defined times (e.g., when the subject first touched the first peg until when s/he dropped the last one) according to the directions provided by Annett. Criteria for discontinuing a trial (e.g., picking up two pegs at once, skipping a peg) were specifically explicated. The total difference in seconds between right and left hands was calculated. Because DI concerns the amount of deviation from the mean rather than the direction, the absolute value of each subject's deviation from the mean was calculated as a measure of his/her DI.

Fingerprinting: Fingerprinting was carried out according to standard inking procedures. Exemplars for the various prints (finger and palm) were provided, along with criteria for acceptance (e.g., unsmudged lines, readable palm area). Ongoing checks of prints were carried out to help ensure that prints were readable for later rating.

AB ridge count ratings: AB ridge counts represent the number of ridges occurring between triradii a (under the index finger) and b (under the middle finger). Ridges were rated and counted according to the procedures followed in Woolf & Gianas (1977). The absolute difference in AB ridge counts between right and left hands was then calculated.

Fingerprint pattern ratings: As followed in Woolf & Gianas (1977), fingerprints were categorized as loops, whorls or arches. For each pair of

homologous fingers for which there was a difference (e.g., right index finger is a whorl, left index finger is a loop), a score of 1 was given. The total fingerprint pattern discrepancy was the sum of these discrepancy scores.

ATD angle ratings: Ratings of maximum ATD angles were made according to guidelines set forth in Penrose (1954). The ATD angle is defined as the angle resulting from lines drawn between the triradii a (under the index finger), d (under the pinkie finger) and t (on the palm). The absolute difference between left and right hands was calculated.

Variable Composition:

In order to reduce the number of individual variables being examined, composite scores were calculated for certain variables:

Working memory: The two working memory measures (Spatial Span and Letter-number sequencing from the WMS-III) were each z-scored and averaged to produce a single working memory composite variable. These two working memory indices have been shown to be highly correlated in standardization samples (e.g., r = .82; Psychological Corporation, 1997).

Analyses:

Hypothesis 1: In order to examine whether the social anhedonia and control groups differ on the basis of rates of obstetric complications and DI, a MANOVA was performed with group (socially anhedonic or control) as the independent variable, and DI and obstetric complications as the dependent variables. If preliminary analyses showed that sex is related to the dependent variables of interest, sex was also to be included as an independent variable. A MANOVA was used

because it was hypothesized, based on the relationship between DI and early environmental insults (e.g., Cannon et al., 1995), that DI and obstetric complications would be related. It was expected that the social anhedonia group would show higher rates for both dependent variables.

Hypothesis 2: In order to assess whether there were both main effects and an interaction effect of social anhedonia status (group), DI and obstetric complications on clinical pathology, three separate groups of analyses were performed.

A. Axis I pathology (SCID): Because the independent variables include both categorical and continuous types, and the dependent variable is categorical, logistic regression was used with Group, DI and obstetric complications as the predictor variables. Logistic regressions were to be performed for SCID mood disorder diagnosis, SCID psychotic disorder diagnosis and SCID substance abuse diagnosis as dependent measures. In light of research discussed previously showing an interaction between genetic liability for schizophrenia-spectrum pathology and environmental insult (e.g., Cannon et al., 1994), it was expected that both main effects and the interaction would be significant in each case.
B. Axis II pathology (IPDE). Because the independent variables are both categorical and continuous, and the dependent variables are continuous, a multivariate multiple regression was used with Group, DI and obstetric complications as the predictor variables, and IPDE Schizoid factor score, IPDE Schizotypal factor score and IPDE Paranoid factor score as the

dependent variables. As discussed above, it was expected that both main effects and the interaction would be significant.

C. General functioning (GAF): For this analysis, since there were both continuous and categorical predictor variables and a single, continuous dependent variable, a univariate multiple regression was performed with Group, DI and obstetric complications as the predictor variables and GAF score as the dependent measure. As discussed above, it was expected that both main effects and the interaction would be significant.

Hypothesis 3: In order to assess whether there were both main effects and an interaction effect of social anhedonia status (group), DI and obstetric complications on neuropsychological functioning, a multivariate multiple regression was performed with Group, DI and obstetric complications as the input variables and CPT score, Working Memory composite score, Logical Memory, Visual Reproduction and General estimated IQ as the dependent variables. This analysis was chosen in order to accommodate both categorical and continuous independent variables, and multiple, continuous dependent variables. As discussed above, it was expected that both main effects and the interaction would be significant.

CHAPTER 9: RESULTS

Demographics:

20 control and 18 social anhedonic males and 21 control and 19 social anhedonic females completed the study; of these subjects, 15 controls and 17 social anhedonics were classified as "minority" (i.e., Black, Hispanic, Asian, or "other") and 26 controls and 20 social anhedonics as "non-minority". There were no significant differences between groups for sex (χ^2 =0.000, p >.05) or race (minority vs. non-minority; χ^2 = .704, p >.05) (see Table 1 for demographics). Analyses were then carried out as planned to determine if sex or race were related to the dependent variables of interest. There were no significant differences for the various measures of DI or rates of obstetric complications between males and females (all ps>.05) or minority/non minority subjects (all ps>.05); therefore, neither sex nor race were statistically included in further analyses.

Measures of DI and Obstetric Complications:

Based on previous research (e.g., Green et al., 1993: Yeo, Gangestad & Daniel, 1993; Yeo et al., 1997), it was predicted that the various measures of DI would be positively correlated; therefore, this study had intended to collapse the DI measures into a single composite variable to be used in further analyses. However, preliminary analysis of the data showed that the DI measures (MPAs, ATD angle, AB ridge count, pegboard scores, and number of fingerprint discrepancies) were not significantly correlated with each other (range of rs = -.146 to .156, all ps >.05) (see Table 2). The lack of correlation was evident both when the total sample was

examined together, and when the sample was analyzed separately by group (social anhedonic and control). In light of this failure to find significant correlations between DI measures, it was decided that it would not make conceptual sense to collapse the measures into a single composite variable.

A second issue that arose in analyzing the data was that maternal report of obstetric complications was only available for 27 subjects (11 social anhedonics and 16 controls), which seriously limited the number of subjects that could be included in analyses involving obstetric complications. Chi-square analyses indicated that there was not a significant difference between groups (χ^2 =.773, p>.05) or sex (χ^2 =.742, p>.05) for the proportion of mothers who completed the obstetric complication questions. However, in light of the low overall number of subjects for whom obstetric history was available (n=27), it was decided that performing analyses using obstetric complications would not yield valid results even in the unlikely event that there was sufficient power. Thus, analyses were conducted including group and DI but omitting obstetric complications (n=78).

Finally, the study had proposed to examine the relationship between DI, obstetric complications and group on SCID psychotic disorder diagnoses if possible. However, only one subject out of 78 had a SCID diagnosis of a psychotic disorder. Therefore, analyses on SCID psychotic disorder diagnoses were omitted.

Hypothesis 1:

In order to examine whether the control and social anhedonia groups differed on the basis of rates of obstetric complications and DI, a series of independent t-tests were performed. The mean ratings for obstetric complications were 1.36 for controls

vs. 1.33 for social anhedonics; results showed that there were no significant differences between groups (t = -.332, p >.05) (see table 3). For measures of DI, it was decided to examine the various measures separately because not all subjects had available fingerprinting data for AB ridge count, ATD angle, and/or fingerprint discrepancies, which limited sample sizes when the variables were analyzed together (see table 4). There were no significant differences between groups for AB ridge count (t = -.734, p >.05), ATD angle (t =-1.651, p >.05), fingerprint discrepancies (t =.318, p >.05), or pegboard scores (t = -.009, p>.05). However, for MPAs, the groups differed significantly, with social anhedonics evidencing significantly higher rates of MPAs than controls (t = -2.003, p<.05) (see table 4). The MPA findings were in line with expectations that subjects at putative genetic risk (i.e., social anhedonics) would show higher rates of DI. When subjects were classified as high vs. low for MPAs (e.g., greater than 4 MPAs vs. 4 or fewer MPAs) in line with Waldrop's suggestions (Waldrop, 1975), only 4 subjects were classified as high-MPA. There were no significant differences between groups for the proportion of high-MPA vs. low-MPA subjects (χ^2 = .011, p>.05). In summary, the control and social anhedonia groups differed significantly on rate of MPAs, but not on the other measures of DI or on obstetric complications.

In light of both the findings that there were significant group differences for MPAs but not for other DI measures, as well as the unavailability of fingerprinting information for all subjects, it was decided to focus further analyses on MPAs; thus, the remaining analyses use MPAs as the sole proxy measure of DI. Previous studies of DI have generally used a single measure such as MPAs, or used two measures in

combination; it is unusual for a study to attempt to use multiple measures as this study had intended to do. Thus, the use of a single proxy measure of DI in this case was not expected to compromise the validity of the assessment of DI, as it was in line with previous studies on the subject.

Hypothesis 2:

In order to examine whether group and DI (MPAs) showed both main effects and an interaction effect on clinical pathology, separate analyses were carried out for Axis 1, Axis 2 and global functioning (GAF) scores.

Axis 1: Preliminary analyses showed that there were significant differences between groups for mood disorders (see table 5), with a higher proportion of social anhedonics having a history of mood disorder diagnoses than controls ($\chi^2 = 8.196$, $p<.005$). There were no significant differences between groups for substance use disorders ($\chi^2 = .412$, $p>.05$) (see table 5). Logistic regressions were then performed with group, MPAs, and the interaction terms as the predictor variables for SCID mood disorder diagnoses and SCID substance use diagnoses. For SCID mood disorder diagnoses, the overall model was significant ($\chi^2 = 12.842$, $p < .01$). However, none of the regression coefficients were significant ($p > .05$), suggesting that while the variables accounted for a significant amount of variance when used in combination, none of them explained a significant amount when considered separately. For SCID substance use disorders, the regression model was not significant ($\chi^2 = 2.287$, $p > .05$).

Due to concerns that depressed subjects in the social anhedonia group might actually represent false positives (i.e., subjects with transient social anhedonia due to

current depression; Blanchard, Horan & Brown, 2001), depressed and non-depressed social anhedonics were also compared on measures of DI and obstetric complications. No significant differences emerged.

In summary, there were significant differences on Axis 1 disorders between groups, with social anhedonics showing higher rates of mood disorders (though not substance use disorders). However, neither MPAs nor their interactions with group had a significant effect on Axis 1 pathology, suggesting that early environmental stressors may not play a significant role in the development of mood disorders in a socially anhedonic sample.

Personality Disorders: Descriptive statistics of personality disorder scores are presented in table 6. A one-way ANOVA with group as the independent variable and IPDE dimensional scores for the Cluster A disorders as dependent variables showed significant differences between groups on all three variables, with social anhedonic subjects higher than controls on Schizotypal ($F = 8.111$; df = 1,76; $p<.01$), Schizoid ($F = 13.207$; df = 1,76; $p<.001$), and Paranoid dimensional scores ($F = 5.695$; df = 1,76; $p<.05$).

A multivariate multiple regression was then performed with group, MPAs and the interaction terms as the predictor variables, and IPDE Schizoid dimensional score, IPDE Schizotypal dimensional score, and IPDE Paranoid dimensional score as the dependent variables. Multivariate tests showed that the overall model was significant for group (F associated with Wilks' $\lambda = 8.615$; df = 3, 60; $p<.001$), MPAs (F associated with Wilks' $\lambda = 2.036$; df = 21,173; $p <.01$) and the Group by MPA interaction (F associated with Wilks' $\lambda = 2.766$; df = 21,173; $p <.001$). Tests of

between-subjects effects revealed that there were no significant main or interaction effects for Schizotypal dimensional scores ($F = 1.796$; df = 15, 62; $p > .05$) or Paranoid dimensional scores ($F = 1.407$; df = 15, 62; $p > .05$). However, for the Schizoid dimensional scores, the corrected model was significant ($F = 8.022$; df = 15, 62; $p < .001$); group ($F = 23.325$; df = 1, 62; $p < .001$), MPAs ($F = 4.746$; df = 7, 62; $p < .001$) and the group by MPA interaction ($F = 6.652$; df = 7, 62; $p < .001$) all showed significant effects in the direction predicted, with social anhedonia and MPAs associated with higher rates of pathology. The interaction between MPAs and group was also associated significantly with pathology, over and above the simple contributions of each variable separately.

Simple Pearson's correlations were then carried out to further examine the relationships between MPAs and Axis 2 dimensional scores. When the two groups were examined separately, different patterns of results emerged (see table 6). For control subjects, there was a significant, positive correlation between MPAs and Paranoid dimensional scores ($r=.40$, $p<.01$) and a significant, negative correlation between MPAs and Schizotypal dimensional scores ($r=-.31$, $p<.05$). There was no correlation between MPAs and Schizoid dimensional score ($r=-.17$, $p>.05$). By contrast, social anhedonic subjects did not show correlations between MPAs and Schizotypal ($r=.25$, $p>.05$) or Paranoid ($r=.03$, $p>.05$) dimensional scores, but did show a significant, positive correlation between Schizoid dimensional score and MPAs ($r=.39$, $p<.05$).

In summary, there were significant differences between groups for Schizoid, Schizotypal and Paranoid dimensional scores, with social anhedonics showing more

pathology than controls. For Schizoid personality disorder, there were also significant effects of MPAs and the group by MPA interaction on Schizoid dimensional scores. Finally, correlation data suggested that MPAs are differentially related to schizophrenia-spectrum personality pathology for the two groups: in controls, they are associated with Schizotypal and Paranoid pathology, while in social anhedonics, they are associated with Schizoid pathology.

Global assessment of functioning (GAF): There were also significant differences between groups for GAF scores, with social anhedonics scoring lower (i.e., more impaired) than controls. The mean GAF score for social anhedonics was 77.62, whereas the mean score for controls was 85.17 ($t = 2.145$, $df = 76$, $p<.05$). These results were in line with the previous research showing that socially anhedonic subjects evidence greater clinical impairment than controls.

A multiple regression was performed with group, MPAs and the interaction terms as the predictor variables, and GAF score as the dependent variable. Results showed that the model was not significant ($p>.05$).

These results show that although socially anhedonic subjects were functioning more poorly than controls, the addition of MPAs and the group by MPA interaction did not add any power in the prediction of global functioning.

Hypothesis 3:

In order to assess for the presence of main and interaction effects of group and MPAs on the various neuropsychological measures, a multivariate multiple regression was performed with CPT d' score, Working Memory Composite score, Logical Memory, Visual Reproduction and General estimated IQ as the dependent variables.

There were no significant results (all ps>.05) (see table 7 for group differences on neuropsychological measures).

Simple Pearson's correlations were also carried out between MPAs and the various neuropsychological variables. Regardless of whether results were examined in the overall sample or by group, there were no significant correlations when correcting for multiple tests. Overall, the results of this study did not suggest a relationship between group, MPAs and neuropsychological functioning.

CHAPTER 10: DISCUSSION

Social anhedonia is a promising predictor of liability for schizophrenia-spectrum disorders. Yet although previous research has shown that high scorers on a social anhedonia questionnaire (the RSAS) develop schizophrenia-spectrum disorders at significantly higher rates than controls, RSAS lacks precision in that the majority of social anhedonics do not develop clinical pathology (Kwapil, 1998). Moreover, schizophrenia is considered to be a disease of neurodevelopmental origin, and social anhedonia has been conjectured to identify risk for the development of schizophrenia. However, research on this specific issue is lacking, and it is as yet unclear whether social anhedonia is actually related to disturbed neurodevelopment.

In the present study, the goal was to address this gap in the literature by examining how social anhedonia was related to measures of disturbed neurodevelopment (i.e., obstetric complications and various measures of DI). It was hypothesized that social anhedonics would show similarly high rates of DI markers and obstetric complications as are seen in individuals at known genetic risk for schizophrenia (i.e., relatives of patients with schizophrenia; Cannon et al., 1995; Green et al., 1989; Satz & Green, 1999). More importantly, it was hypothesized that combining social anhedonia with neurodevelopmental risk factors would allow more accurate prediction of which individuals were at highest risk for the type of clinical and neuropsychological impairment associated with schizophrenia-spectrum pathology. Based on evidence that genetic liability and environmental insults may combine in an interactive manner to increase risk for pathology (e.g., Cannon et al.,

1994), it was predicted that social anhedonia, obstetric complications and DI would show both main and interaction effects on the variables of interest.

Consistent with the hypothesis that social anhedonia would be associated with greater clinical pathology, the present study found higher rates of mood disorders and Schizoid, Paranoid and Schizotypal dimensional scores, as well as lower overall functioning in social anhedonics compared to controls. These findings support the validity of social anhedonia as an indicator of putative genetic risk for schizophrenia; the results show that a group identified purely by self-report of social anhedonia display clinical symptoms and global pathology when clinically interviewed. In addition, the findings are in line with prior research showing higher rates of pathology among socially anhedonic college students (e.g., Kwapil, 1998). The results of this study are particularly important, as they indicate that prior research on social anhedonia in college freshmen appears to extend to individuals recruited from the community.

The low number of Axis 1 psychotic diagnoses found in these 18-year olds was also in line with past research; other psychometric high-risk studies (e.g., Kwapil, 1998) also found no differences in Axis 1 schizophrenia-spectrum pathology at baseline, though significant differences emerged at 10-year follow-up. Therefore, it would be interesting to repeat this study in 10 years, when the majority of subjects will have passed the period of risk for onset of a schizophrenia-spectrum disorder. At the current time point, the higher rates of mood disorders and personality pathology, as well as the lower GAF scores seen in the social anhedonia group are consistent with the possibility that compared to controls, a greater number of socially anhedonic

subjects in this study are in the prodromal period for a schizophrenia-spectrum disorder.

With regard to DI, it was expected that there would be higher rates of the various DI markers in the social anhedonia group. In line with expectations, this study found higher rates of minor physical anomalies, an index of DI, among social anhedonics. These findings are also consistent with Meehl's hypothesis that social anhedonia is, in fact, a putative measure of genetic liability for schizophrenia-spectrum disorders (Meehl, 1962). This hypothesis would suggest that social anhedonics should therefore show increased rates of DI that are similar to those seen in individuals with schizophrenia and their family members. However, the various measures of DI were not significantly correlated, and no significant group differences were found among the other DI measures (AB ridge count, ATD angle, pegboard scores, and fingerprint discrepancies). These latter findings are difficult to explain, as prior research (e.g., Green, Bracha, Satz & Christenson, 1994; Yeo, Gangestad & Daniel, 1993; Yeo et al., 1997) has generally found different measures of DI to be positively correlated. Furthermore, a body of research has shown significant differences between those individuals at known genetic risk for schizophrenia-spectrum disorders across all measures of DI.

In light of the lack of group differences between many of the DI measures, and the lack of correlation between them, it was decided to use MPAs as the sole measure of DI. It was not expected that this decision would compromise the validity of the assessment; as discussed previously, previous studies of DI and schizophrenia have typically used one or two measures rather than attempting to combine several

measures as this study had intended to do. However, since the various measures of DI do assess slightly different processes of aberrant neurodevelopment, it is unclear whether focusing the assessment on a single measure (MPAs) rather than combining multiple different measures results in a slightly different assessment of DI. Moreover, it is not at all clear why the multiple measures of DI included in this study were uncorrelated, and why many of them did not differ between control and socially anhedonic subjects.

One possible explanation for the lack of group differences and intercorrelations for many of the DI measures is that, with the exception of one study (Rosa et al., 2000), prior research on schizophrenia and DI has focused either on individuals with schizophrenia or family members of such individuals, rather than subjects identified as "at-risk" through psychometric high-risk paradigms such as the one used in this study. Thus, it is unclear whether such prior findings apply to the group of subjects used in this study; it is not certain whether the two methods of subject identification result in similar groups. Furthermore, it is possible that psychometric identification of subjects may result in certain false positives (e.g., subjects misidentified as socially anhedonic due to transient depression; Blanchard, Horan & Brown, 2001), and that this may drive down the effect sizes for group differences.

In this study, there was a significantly higher proportion of social anhedonics with past or present mood disorders. Thus, it is possible that some of these subjects were misidentified as socially anhedonic due to their depression. However, it is also possible that the higher rates of depression among the socially anhedonic subjects are

due to the fact that depression is often seen in the prodrome for schizophrenia-spectrum disorders (Kim-Cohen et al., 2003). Post-hoc analyses within the social anhedonia group did not shed much light on these various explanations, as there were no significant differences between social anhedonics with or without a lifetime history of depression on any of the DI measures. Further research would benefit from assessing social anhedonia at multiple time-points in order to identify a group of subjects with stable, primary social anhedonia.

Another source of explanation for the superior performance of minor physical anomalies over other DI measures is the specific aberrant processes reflected by the different DI markers. Both handedness (pegboard task) and fluctuating asymmetries (AB ridge count, ATD angle, and fingerprint asymmetries) appear to develop during a longer window of sensitivity to environmental perturbations that may extend into the second trimester (Reilly et al., 2001; Yeo et al., 1993). By contrast, minor physical anomalies are mainly formed during the first trimester (Schiffman et al., 2002). In addition, handedness and fluctuating asymmetries have been conjectured to result mostly from variations in growth rates (Yeo et al., 1993), while different types of minor physical anomalies may represent either slowed development (e.g., wide-spaced eyes, low-seated ears) or disrupted development (e.g., malformed ears) (Yeo, Gangestad & Daniel, 1993). Thus, it is possible that minor physical anomalies may be measuring a set of phenomena that has a more time-limited period during which disruption could occur (i.e., mostly first trimester vs. first and second trimesters). However, minor physical anomalies may also be affected by a more varied set of phenomena than other DI markers (e.g., slowed development or disrupted

development vs. just variations in growth rates). These characteristics may make minor physical anomalies differentially more sensitive to developmental disruption that contributes to schizophrenia-spectrum pathology in the present sample of psychometrically-identified 18-year olds. However, it is unclear why psychometrically-identified at-risk subjects would differ from those at known genetic risk, such as family members of patients with schizophrenia. Further studies will be needed to clarify the validity and cause of these findings.

Finally, difficulty obtaining readable palm prints for certain subjects resulted in lower numbers of subjects available for analysis on certain fingerprinting measures. These reduced numbers (i.e., 50 subjects for ATD angle, 69 for AB ridge count) may have further contributed to the failure to find significant group differences on those measures. However, this possibility is fairly unlikely, as effect sizes between groups for those measures were generally small.

With regard to obstetric complications, this study hypothesized that social anhedonics would have higher rates of obstetric complications, and that obstetric complications would be related to the various DI measures. However, results showed that the control and social anhedonia groups did not differ. In addition, there was no correlation between obstetric complications and the various measures of DI. These findings were surprising given previous studies that have shown higher rates of obstetric complications among individuals with known aberrant fetal development (Smith et al., 1998). In fact, it has been suggested that disruptions in fetal development such as the disruptions that result in DI markers may actually predispose the fetus towards an eventual outcome of a complicated pregnancy and birth

(Waddington et al., 1998; Smith et al., 1998). It is possible that in this sample, the validity of the data on obstetric complications was seriously compromised by the small number of mothers who completed the questions (n = 27 vs. a total n of 78). In addition, it is unclear whether the mothers who did agree to complete the questions were representative of the sample as a whole, or whether they were biased in some way (e.g., those who had had complicated pregnancies and deliveries being more or less likely to agree to participate). Thus, it is difficult to draw conclusions about these findings.

This study also hypothesized that, consistent with the literature on genetic and obstetric risk factors (e.g., Cannon et al., 1993; Schiffman et al., 2002), group, DI and obstetric complications would show both main and interactive effects on clinical and neuropsychological impairment. As mentioned earlier, there was only one psychotic disorder diagnosis, so it was not possible to analyze psychotic disorder results. For the other clinical and neuropsychological measures, across all analyses involving obstetric complications, there were no significant findings. However, as discussed in the results section, these analyses were significantly limited by small sample sizes (e.g., total N of 27), and are therefore likely unreliable. When only group and MPA were considered in the analyses, different patterns of results emerged across the various domains of functioning (i.e., Axis 1 disorders, personality disorders, global functioning and neuropsychological performance).

For Axis 1 pathology (mood and substance use disorders) and global functioning, there were significant differences between social anhedonics and controls, but no effects of minor physical anomalies or the Group x minor physical

anomalies interaction. These group results are consistent with the hypothesis that social anhedonia is a measure of putative risk for schizophrenia-spectrum disorders, and is in line with prior research (e.g., Kwapil, 1998; Clementz, Grove, Katsanis & Iacono, 1991; Grove et al., 1991; Katsanis et al., 1990). However, the failure to find significant effects for the minor physical anomalies and the Group x minor physical anomalies interaction is surprising. One possible explanation is that while past studies (e.g., Waldrop, 1975) have found a high number of minor physical anomalies to be associated with clinical pathology, only four subjects in this study could be classified as "high" for number of minor physical anomalies (i.e., greater than 4). A future study might benefit from a larger pool of subjects, in order to ensure a sufficient number of "high minor physical anomalies" individuals to adequately examine the effects of minor physical anomalies and the Group x minor physical anomalies interaction on Axis 1 pathology and global functioning.

In terms of personality disorders, this study had predicted that there would be main and interaction effects of group and DI on schizophrenia-spectrum personality pathology (e.g., Schizoid, Schizotypal and Paranoid dimensional scores). Results showed that there were significant group differences for Schizotypal and Paranoid dimensional scores, but no significant effects of minor physical anomalies or the group x minor physical anomalies interaction. For the Schizoid dimensional scores, there were significant main and interactive effects of group and minor physical anomalies, such that both factors conferred increased risk for Schizoid pathology, and the two factors together showed a positive interaction effect. These findings follow the expected pattern of results, and are in line with research showing both main and

interactive effects of genetic liability and environmental insult (e.g., Cannon et al., 1993) on expression of clinical schizophrenia-spectrum pathology. Furthermore, they suggest that group and minor physical anomalies may play differential roles across the different personality disorders.

Interestingly, these findings also suggest that the differential results may cleave to the division of positive and negative symptoms. Schizoid personality disorder could be characterized as representing mainly "negative" symptoms, while Paranoid and Schizotypal personality disorders could be characterized as representing more "positive" symptoms. A variety of studies have supported the notion that positive and negative symptoms are relatively unrelated, and may represent different pathophysiological processes (Eaton et al., 1995). Thus, the different patterns of results found across personality disorders in this study may simply be due to different causal pathways for the disorders. Negative symptoms have been said to represent a separate and independent domain of symptoms from positive symptoms or social functioning (Lenzenweger & Dworkin, 1996; Lenzenweger, Dworkin & Wethington, 1989). On a neurobiological level, research has suggested that negative symptoms may stem from underactivity of dopamine in the frontal lobes (e.g., Andreasen et al., 1992), while positive symptoms may be the result of dopamine overactivity (Fowles, 1992). Moreover, it has been conjectured that negative symptoms may be more closely related to genetic predisposition for schizophrenia than positive symptoms (e.g., Dworkin et al., 1998; Tsuang, 1993), and negative symptoms may better identify relatives of patients with schizophrenia than other types of symptoms (e.g., Kendler et al., 1996). Thus, it is possible that social anhedonia and DI may play a

unique role in the development of "negative" schizophrenia-spectrum pathology such as Schizoid personality disorder symptoms, but not in the more "positive" Schizotypal or Paranoid personality disorder symptoms because the former is more closely tied to the underlying genetic and neurobiological pathway of schizophrenia-spectrum liability (Tsuang, 1993).

The possibility that genetic liability and DI may play a unique role in Schizoid-type pathology dovetails with Cannon's theory about the interaction of genetic risk with environmental stressors (Cannon et al., 1989). This study found different relationships between DI and schizophrenia-spectrum pathology between groups, such that higher rates of minor physical anomalies were associated with greater Schizoid symptoms in the social anhedonia group, but not with Paranoid or Schizotypal symptoms. By contrast, minor physical anomalies were associated with higher rates of Paranoid symptoms and lower rates of Schizotypal symptoms in the control group, but not with Schizoid symptoms. While the inverse association of minor physical anomalies and Schizotypal symptoms in the control group is certainly difficult to explain, the divergent relationships between minor physical anomalies and positive and negative symptoms for Schizoid and Paranoid disorders between groups is striking. For those at putative genetic risk (i.e., social anhedonics), minor physical anomalies were associated with the more negative symptomatology that has been conjectured to lie close to the genetic and neurobiology of schizophrenia. However, in the absence of genetic risk, minor physical anomalies were associated with more positive symptomatology, non-specific to schizophrenia. The idea that minor physical anomalies, a proxy measure of environmental stress, may play differential

roles depending on the presence or absence of genetic liability is in line with Cannon's hypothesis that early environmental insults may have different consequences depending on the presence or absence of a genetic vulnerability.

On measures of neuropsychological functioning, neither group nor minor physical anomaly measures were related to the variables of interest. These results were surprising given both predictions made based on theoretical models (e.g., minor physical anomalies as evidence of early disruptions in brain development that would be expected to have an impact on the developing brain) and in light of studies on the subject. Research has suggested that measures of DI such as minor physical anomalies are associated with neuropsychological impairment on a variety of cognitive tests including working memory and general cognitive ability (e.g., Guy et al., 1983; Yeo et al., 2000). In addition, a large body of evidence supports the presence of neuropsychological pathology in individuals at genetic risk (e.g., those with schizophrenia and their unaffected family members; Faraone et al., 1994; Cannon et al., 1994; Faraone et al., 2000). Moreover, it has been suggested that such neurocognitive impairments may be a good indicator of schizotypy, as they are closer to the endophenotype, and are presumably more closely linked to early neural development (Faraone et al., 2001). Thus, the failure to find significant effects of social anhedonia, minor physical anomalies or obstetric complications on neuropsychological functioning in this study is somewhat puzzling; it is difficult to argue that sample characteristics such as response bias (e.g., only cognitively intact subjects were able to make and keep appointments) can fully explain these results, as many of the impairments expected would have been fairly subtle.

One plausible hypothesis is that, as was the case with the various measures of DI, the relationship between neuropsychological functioning and genetic and environmental risk factors in a sample of psychometrically-identified high-risk individuals is different in some way from that seen in individuals identified as high risk through family history methods. Alternatively, it is possible that schizophrenia is associated with neurocognitive deterioration once the disease sets in (Keshavan, 1999), and in this group of subjects who had not yet developed frank psychosis, group differences were not yet visible. Clearly, more research is needed to clarify these questions.

CHAPTER 11: CONCLUSIONS

This study examined the relationship between various factors that are known to independently predict risk for schizophrenia-spectrum pathology: putative genetic risk as indexed by psychometric identification of social anhedonia; obstetric complications; and developmental instability (DI). Results showed that rates of one of the measures of DI, minor physical anomalies (MPAs) were significantly higher in the social anhedonia group, as were Axis 1 Mood Disorder diagnoses and Schizoid, Schizotypal and Paranoid dimensional scores; global functioning as measured by GAF scores was significantly worse among social anhedonics. More importantly, the study found that group and DI (as indexed by MPAs) had significant main effects and an interaction in the prediction of Schizoid personality disorder dimensional scores. There was also a disjunction between the manner with which DI and personality disorder pathology were related across groups, with DI being associated with increased Schizoid characteristics within the social anhedonia group and increased Paranoid characteristics within the control group; this disjunction suggests that DI may be differentially related to type of pathology depending on degree of genetic risk. Moreover, the finding of minor physical anomalies being associated with increased pathology in social anhedonics supports the conjecture that measures of neurodevelopment can enhance the detection of schizophrenia-spectrum pathology within a group of individuals at putative genetic risk.

Although group, DI and obstetric complications did not show the predicted relationships to neuropsychological impairment, the above findings are of note. A

significant literature has linked DI and obstetric complications to risk for schizophrenia-spectrum disorders. In addition, social anhedonia has been widely supported as a putative measure of genetic liability. However, the integration of these two bodies of research has been relatively unexplored; this study's findings are therefore interesting, as they allow examination of the extent to which the two lines of previous research mesh. The finding that only MPAs and not the other measures of DI were significantly different between groups suggests that, at least among this sample of psychometrically-identified individuals, certain DI characteristics may be more sensitive to genetic liability. Furthermore, among this sample, putative genetic risk and presumed environmental insult showed main and interaction effects on negative Schizoid pathology, but not on more positive symptom pathology (Paranoid or Schizotypal), or on neuropsychological or global functioning.

As discussed previously, one possible explanation for these variable findings is that negative symptom-type pathology indexed by Schizoid characteristics may lie closer to the genetic and neurobiological substrates of schizophrenia-spectrum disorders, and thus may be more closely related to DI and social anhedonia than the other variables. More research combining psychometric high-risk paradigms with measures of environmental insult is clearly needed before firm conclusions may be drawn. However, the results of this study offer a promising starting point.

CHAPTER 12: LIMITATIONS AND FUTURE DIRECTIONS

One initial limitation of this study was the difficulty obtaining maternal report of obstetric complications, which resulted in only about a third of subjects providing those data. The problem of missing data and small sample sizes for obstetric complications greatly reduced power, and also raised questions about the generalizability of the findings. On a similar note, difficulties obtaining readable prints for all subjects on the fingerprinting measures may have also limited power and generalizability for analyses on those measures as well.

Recruitment methods used in this study involved obtaining a random sample of 18-year olds residing within 15 miles of the University of Maryland. This recruitment strategy resulted in an ethnically and socioeconomically diverse group of individuals. The initial screening measure, which was completed by subjects at home, had an approximate response rate of 70%. Subsequent evaluations involved traveling to the University of Maryland for more lengthy assessments, and had a lower response rate of about 50% (from the smaller pool of subjects invited to complete these in-person assessments). Thus, of the initial group of subjects, a minority ended up completing all of the assessments used in this study. There were no significant differences in terms of clinical or neuropsychological characteristics between subjects who completed the in-person portion of the larger study but not this study and subjects who completed both. However, it is not clear whether the individuals who chose not to complete any of the in-person assessments did so for reasons related to the variables of interest (i.e. clinical pathology or

neuropsychological impairments that made it difficult for them to complete their questionnaires or to keep appointments). It is possible that the smaller number of subjects who were able to complete and mail their questionnaires and then schedule and keep appointments were in some way more highly functional than the subjects who did not complete the study. If this were the case, it may have resulted in an artificially high-functioning group, which could have biased results. This possibility is somewhat limited, however, by the lower clinical ratings of global functioning and the presence of Axis 1 and personality pathology in the social anhedonia group.

Another issue faced by this study was that the subjects studied were 18, and may have been only just entering the period of risk for development of observable schizophrenia-spectrum clinical pathology, particularly for Axis 1 disorders. A previous study of socially anhedonic college undergraduates found no differences in schizophrenia-spectrum pathology between the anhedonia and control groups at baseline. However, at 10-year follow-up, 24% of the anhedonia group had a schizophrenia-spectrum disorder compared with 1% of controls (Kwapil, 1998). It has been suggested that the effects of social anhedonia on pathology and functioning may become more pronounced as individuals move away from their family home and experience less social support, contact and feedback to counter their cognitive slippage and unusual ideas and experiences (Kwapil, 1998). This study may have evaluated subjects too early to fully detect different clinical outcomes between groups, as the assessments took place during the baseline assessment phase of a larger, five-year longitudinal study. Based on prior research, it is expected that group differences will only increase as time progresses. Thus, this study and future research

should attempt to evaluate subjects at multiple time-points to explore the potentially changing relationships between risk factors and pathology across adolescence and young adulthood.

Related to the above discussion about the age of the subjects is the possibility that so-called "prodromal" features of schizophrenia such as psychotic-like experiences may be non-specific to schizophrenia when measured in adolescence. For example, one study found that fully 75% of a sample of adolescents indicated the presence of one or more attenuated positive symptoms (magical ideation or perceptual aberrations), and half of the subjects had two or more of the symptoms (McGorry et al., 1995). These results highlight the importance of measuring schizophrenia-spectrum pathology across multiple time-points to ensure the identification of enduring symptoms rather than transient, age-normative experiences, something that future studies would benefit from observing.

A final limitation of this study is the restriction of measures of environmental insult to the pre-and peri-natal periods. A significant body of literature has shown the critical role that the type of obstetric complications and early developmental insults that give rise to DI markers can play in the eventual development of schizophrenia. However, there is also some evidence that later events, such as childhood head injury, may also be associated with higher rates of schizophrenia (Abdel Malik et al, 2003). Thus, future studies might benefit from including multiple domains of environmental insult, including both pre- and post- birth events.

Table 1
Demographic Characteristics of Controls (n = 41) and Social Anhedonics (n = 37):

	Control n (%)	Social Anhedonia n (%)
Sex:		
Male	20 (48.8%)	18 (48.7%)
Female	21 (51.2%)	19 (51.4%)
Ethnicity:		
White	26 (63.4%)	19 (51.4%)
Black	10 (24.4%)	16 (43.2%)
Asian	1 (2.4%)	1 (2.7%)
Hispanic	3 (7.3%)	1 (2.7%)
Other	1 (2.4%)	0 (0.0%)
Minority vs. Non-minority:		
Minority	15 (36.6%)	17 (45.9%)
Non-minority	26 (63.4%)	20 (54.1%)

Table 2
Correlations Between Measures of Developmental Instability Across All Subjects:

Correlation coefficients (rs)
(n)

	Minor Physical Anomalies	Fingerprint discrepancies	AB ridge count	ATD angle
Pegboard task	-.13 (78)	-.02 (78)	.00 (69)	.11 (50)
ATD angle	.16 (50)	-.15 (50)	.15 (49)	
AB ridge count	-.03 (69)	.11 (69)		
Fingerprint discrepancies	-.04 (78)			

Note: numbers in parentheses denote the number of subjects for each correlation

Table 3
Means for Control Subjects and Social Anhedonia Subjects for Measures of Developmental Instability:

	Control	Social Anhedonia
	Mean (SD) (n)	Mean (SD) (n)
Minor Physical Anomalies	1.83 (1.75) (41)	2.68 (1.99) * (37)
AB ridge count	3.89 (2.96) (36)	4.48 (3.76) (33)
ATD angle	2.61 (2.22) (28)	3.95 (3.53) (22)
Pegboard task	0.81 (0.46) (41)	0.81 (0.70) (37)
Fingerprint discrepancy	1.17 (0.77) (41)	1.11 (0.97) (37)

* p <.05

Table 4
Axis 1 Mood and Substance Use Disorders for Social Anhedonia Subjects (n = 37) and Control Subjects (n = 41).

	Control n (%)	Social Anhedonia n (%)
Mood Disorder	5 (12%)	15 (41%) *
Substance Use Disorder	9 (22%)	6 (16%)

* $p < 0.01$

Table 5
Personality Disorder Dimensional Scores for Social Anhedonia Subjects (n = 37) and Control Subjects (n = 41).

	Control Mean (SD)	Social Anhedonia Mean (SD)
Schizoid Personality Disorder	0.24 (0.62)	1.49 (2.09) ***
Schizotypal Personality Disorder	0.32 (0.69)	1.03 (1.42) **
Paranoid Personality Disorder	0.34 (0.88)	1.08 (1.75) *

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

Table 6
Correlations between Minor Physical Anomalies (MPAs) and Personality Disorder Dimensional Scores by Group:

	Correlations (rs) with MPAs		
	Schizoid Dimensional Score	Schizotypal Dimensional Score	Paranoid Dimensional Score
Controls (n = 41)	-.17	-.31 *	.40 *
Social Anhedonics (n = 37)	.39 *	.25	.03

*p < .05

Table 7
Group Means on Neuropsychological Measures for Controls (n = 41) and Social Anhedonics (n = 37):

	Control Mean (SD)	Social Anhedonia Mean (SD)
Estimated IQ (z-score)	0.041 (0.816)	-0.454 (0.936)
Working Memory composite (z-score)	-0.004 (0.796)	0.005 (0.802)
CPT d’	2.089 (0.786)	2.166 (1.077)
Digit Span Forward	10.71 (2.26)	10.16 (2.33)
Digit Span Backward	7.76 (2.86)	7.00 (2.00)

Institutional Review Board
University of Maryland
College Park, MD 20742

Approval Document for Expedited Review of Non-Exempt Projects

PLEASE NOTE: Institutional Review Board approval of this project expires on **May 31, 2003.

X Initial Application Renewal Application

PRINCIPAL INVESTIGATOR: Dr. Jack Blanchard
CO-INVESTIGATOR: Not Applicable
STUDENT INVESTIGATOR: Minu Aghevli
DEPARTMENT OR PROGRAM: Department of Psychology
PROJECT TITLE AND IRB NUMBER:
"Early Development, Traits and Psychological Functioning" (IRB Number 01227)

The University IRB reviewed the above-mentioned project on **May 3, 2002**, in accordance with Public Health Service grant policy as defined in "The Institutional Guide to DHHS Policy on Protection of Human Subjects," 12-1-71, and in Title 45, Code of Federal Regulations, Part 46. The University IRB is:

Joan A. Lieber, Professor, Special Education, CO-CHAIRPERSON
Marc A. Rogers, Associate Professor, Kinesiology, CO-CHAIRPERSON
Denise A. Andrews, University Counsel, Office of Legal Affairs
Ethelyn Bishop, Non-University Member
Sacared A. Bodison, M.D., Physician, Health Services, Health Center
Margaret W. Bridwell, M.D., Director, Student Health, Health Center
Ms. Judith Carrithers, J.D., Non-University Member
Jude A. Cassidy, Professor, Psychology
Jane Doussard-Roosevelt, Research Associate Professor, Human Development
Ellen S. Fabian, Associate Professor, Counseling and Personnel Services
Gary LaFree, Professor, Criminology and Criminal Justice
Kenneth Jennings, Jr., Non-University Member
Margaret McLaughlin, Associate Director, Special Education
George Perkins, Non-University Member
Samuel M. Turner, Professor, Psychology
Cynthia Tuttle, Assistant Professor, Nutrition and Food Science
Eric Wish, Director, Center for Substance Abuse Research

The IRB effected an independent determination of: (1) the rights and welfare of the individual or individuals involved, (2) the appropriateness of the methods used to secure informed consent, and (3) the risks and potential benefits of the investigation. The IRB has concluded that proper safeguards have been taken by the principal investigator, as stated in the research proposal. The IRB approves this project as conforming to University and Public Health Service Policy in protecting the rights of the subjects.

Joan Lieber

Marc A. Rogers, IRB Co-Chair **OR** **Joan A. Lieber, IRB Co-Chair**

The Principal Investigator (and Co-Investigator and Student Investigator, where appropriate), in signing this report, agree to follow the recommendations of the IRB, to notify the Office of the Vice President of Research of any additions to or changes in procedure subsequent to this review, to provide information on the progress of the research on an annual basis, and to report any instances of injuries to subjects and unanticipated problems involving risks to subjects or others. Any consent forms used in connection with this project must be retained by the Principal Investigator for three years after completion of the research.

Principal Investigator (or Faculty Advisor) **Co-Investigator**

Student Investigator

PLEASE RETURN ONE SIGNED COPY TO:
IRB OFFICE, ROOM 2100, BLAIR LEE BUILDING, CAMPUS-- 5121. Thank you.

Institutional Review Board
University of Maryland
College Park, MD 20742

Renewal Application Approval Document for Expedited Review of Non-Exempt Projects

******PLEASE NOTE: Institutional Review Board approval of this project expires on May 31, 2004******

PRINCIPAL INVESTIGATOR:	Jack Blanchard, Ph.D.
CO-INVESTIGATOR:	not applicable
STUDENT INVESTIGATOR:	Minu Aghevli
DEPARTMENT OR PROGRAM:	Department of Psychology
PROJECT TITLE AND IRB NUMBER:	

01227---Early Development, Traits, and Psychological Functioning

The University IRB reviewed the above-mentioned project on **Wednesday, May 7, 2003**, in accordance with Public Health Service grant policy as defined in "The Institutional Guide to DHHS Policy on Protection of Human Subjects," 12-1-71, and in Title 45, Code of Federal Regulations, Part 46.

University of Maryland, College Park Institutional Review Board
Joan A. Lieber, Professor, Special Education, CO-CHAIRPERSON
Phylis Moser-Veillon, Professor, Nutrition and Food Science, CO-CHAIRPERSON
April Falcon Doss, Non-University Member, IRB SECRETARY
Denise A. Andrews, University Counsel, Office of Legal Affairs
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Gary LaFree, Professor, Criminology and Criminal Justice
Margaretha S. Lucas, Ph.D., Counseling Center
Kenneth Jennings, Jr., Non-University Member
Margaret McLaughlin, Associate Director, Special Education
Samuel M. Turner, Professor, Psychology
Eric Wish, Center for Substance Abuse Research

The IRB effected an independent determination of: (1) the rights and welfare of the individual or individuals involved, (2) the appropriateness of the methods used to secure informed consent, and (3) the risks and potential benefits of the investigation. The IRB has concluded that proper safeguards have been taken by the principal investigator, as stated in the research proposal. The IRB approves this project as conforming to University and Public Health Service Policy in protecting the rights of the subjects.

Phylis Moser-Veillon

Phylis Moser-Veillon, IRB Co-Chairperson OR **Joan A. Lieber, IRB Co-Chairperson**

The Principal Investigator (and Co-Investigator and Student Investigator, where appropriate), in signing this report, agree to follow the recommendations of the IRB, to notify the Office of the Vice President of Research of any additions to or changes in procedure subsequent to this review, to provide information on the progress of the research on an annual basis, and to report any instances of injuries to subjects and unanticipated problems involving risks to subjects or others. Any consent forms used in connection with this project must be retained by the Principal Investigator for three years after completion of the research.

Principal Investigator (or Faculty Advisor) **and** **Co-Investigator**

Minu Aghevli

Student Investigator

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IRB OFFICE, ROOM 2100, BLAIR LEE BUILDING, CAMPUS--- 5121. Thank you

SCREENING MEASURE

S = Revised Social Anhedonia Scale item
M = Magical Ideation Scale item
P = Perceptual Aberration Scale item
I = Infrequency Scale item
GTS = General Temperament Scale item (not used in the present study)

Items are shown scored in the "deviant" direction

FEELINGS AND PREFERENCES SCALE

INSTRUCTIONS:
Listed below are a series of statements a person might use to describe his/her feelings, attitudes, interests, and other characteristics. Read each statement and decide how well it describes you. If the statement is **TRUE** or **MOSTLY TRUE**, fill in the bubble to the left of the T. If it is **FALSE** or **MOSTLY FALSE**, fill in the bubble next to the F.

If an item refers to an experience you have had **ONLY WHEN TAKING DRUGS, ALCOHOL, OR MEDICATIONS**, mark it as if you have **NOT** had that experience.

Please answer **EVERY STATEMENT**, even if you are not completely sure of the answer.

GTS		1.	I would describe myself as a tense person.
S	F	2.	I feel pleased and gratified as I learn more and more about the emotional life of my friends.
GTS		3.	At times I've done some petty thievery.
S	T	4.	I am usually content to just sit alone, thinking and daydreaming.
S	F	5.	When someone close to me is depressed, it brings me down also.
S	T	6.	Although I know I should have affection for certain people, I don't really feel it.
GTS		7.	I always try to be fully prepared before I begin working on anything.
GTS		8.	I greatly dislike it when someone breaks accepted rules of good behavior.
GTS		9.	I spend a good deal of my time just having fun.
M	F	10.	I almost never dream about things before they happen.

GTS		11.	Often life feels like a big struggle.
GTS		12.	I can make a game out of some things that others consider work.
I	F	13.	Sometimes when walking down the sidewalk, I have seen children playing.
M	T	14.	I have sometimes felt that strangers were reading my mind.
GTS		15.	I often feel nervous and "stressed."
GTS		16.	My anger frequently gets the best of me.
GTS		17.	I am usually alert and attentive.
GTS		18.	The way I behave often gets me into trouble on the job, at home, or at school.
GTS		19.	I rarely, if ever, do anything reckless.
P	T	20.	I have felt that my body and another person's body were one and the same.
GTS		21.	I am sometimes troubled by thoughts or ideas that I can't get out of my head.
GTS		22.	Taking care of details is not my strong point.
GTS		23.	I frequently find myself worrying about things.
GTS		24.	I've been told that I work too hard.
GTS		25.	I am not an "impulsive buyer."
GTS		26.	I work just hard enough to get by.
P	T	27.	Occasionally I have felt as though my body did not exist.
GTS		28.	I seem to be able to remain calm in almost any situation.
M	T	29.	I sometimes have a feeling of gaining or losing energy when certain people look at me or touch me.
M	F	30.	When introduced to strangers, I rarely wonder whether I have known them before.
GTS		31.	I worry about terrible things that might happen.
M	T	32.	I have sometimes sensed an evil presence around me, although I could not see it.
M	T	33.	At times, I have felt that a professor's lecture was meant especially for me.
M	T	34.	I have wondered whether the spirits of the dead can influence the living.
M	T	35.	I have worried that people on other planets may be influencing what happens on Earth.

GTS		36.	I don't keep particularly close track of where my money goes.
S	T	37.	My relationships with other people never get very intense.
GTS		38.	My pace is usually quick and lively.
GTS		39.	When I decide things, I always refer to the basic rules of right and wrong.
S	T	40.	I prefer hobbies and leisure activities that do not involve other people.
I	T	41.	I cannot remember a single occasion when I have ridden on a bus.
M	T	42.	People often behave so strangely that one wonders if they are part of an experiment.
GTS		43.	I lead a very interesting life.
GTS		44.	I like to take chances on something that isn't sure, such as gambling.
M	T	45.	I have sometimes been fearful of stepping on sidewalk cracks.
S	F	46.	When others try to tell me about their problems and hangups, I usually listen with interest and attention.
M	F	47.	Good luck charms don't work.
GTS		48.	I live a very full life.
S	F	49.	Although there are things that I enjoy doing by myself, I usually seem to have more fun when I do things with other people.
GTS		50.	I can easily find ways to liven up a dull day.
GTS		51.	People would describe me as a pretty enthusiastic person.
GTS		52.	I get pretty excited when I'm starting a new project.
GTS		53.	I don't get very upset when things go wrong.
S	F	54.	There are things that are more important to me than privacy.
S	T	55.	Making new friends isn't worth the energy it takes.
P	F	56.	My hands or feet have never seemed far away.
GTS		57.	I am a serious-minded person.
GTS		58.	Sometimes life seems pretty confusing to me.
P	T	59.	I can remember when it seemed as though one of my limbs took on an unusual shape.
GTS		60.	Things seem to bother me less than most other people.
S	T	61.	I never had really close friends in high school.
GTS		62.	I would not use others' weaknesses to my own advantage.
GTS		63.	When I resent doing something, I sometimes deliberately make mistakes.
GTS		64.	I believe in playing strictly by the rules.

P	T	65.	I have felt as though my head or limbs were somehow not my own.
P	T	66.	I sometimes have had the feeling that my body is abnormal.
P	T	67.	I have sometimes felt that some part of my body no longer belongs to me.
GTS		68.	I am sometimes "on the go" so much that I wear myself out.
S	F	69.	When things are going really good for my close friends, it makes me feel good too.
M	T	70.	I have sometimes had the passing thought that strangers are in love with me.
GTS		71.	I have days that I am very irritable.
M	T	72.	Some people can make me aware of them just by thinking about me.
GTS		73.	I worry too much about things that don't really matter.
GTS		74.	I sometimes get all worked up as I think about the day's events.
P	T	75.	Now and then, when I look in the mirror, my face seems quite different than usual.
GTS		76.	Sometimes I feel "on edge" all day.
S	T	77.	I prefer watching television to going out with other people.
M	T	78.	I think I could learn to read others' minds if I wanted to.
GTS		79.	Small annoyances often irritate me.
M	F	80.	I have never had the feeling that certain thoughts of mine really belonged to someone else.
S	F	81.	A car ride is much more enjoyable if someone is with me.
		82.	I often have difficulty sleeping because of my worries.
M	F	83.	Numbers like 13 and 7 have no special powers.
P	T	84.	It has seemed at times as if my body was melting into my surroundings.
M	T	85.	I have felt that there were messages for me in the way things were arranged, like in a store window.
P	T	86.	Sometimes I have had feelings that I am united with an object near me.
P	F	87.	I have never felt that my arms or legs have momentarily grown in size.
S	F	88.	I like to make long distance phone calls to friends and relatives.
GTS		89.	I am often playful around other people.
S	T	90.	In many ways, I prefer the company of pets to the company of people.
P	T	91.	Sometimes I feel like everything around me is tilting.
GTS		92.	Little things upset me too much.

S	T	93.	When I am alone, I often resent people telephoning me or knocking on my door.
GTS		94.	I sometimes feel angry for no good reason.
S	F	95.	It made me sad to see all my high school friends go their separate ways when high school was over.
I	F	96.	At times when I was ill or tired, I have felt like going to bed early.
GTS		97.	Other people sometimes have trouble keeping up with the pace I set.
GTS		98.	I'll take almost any excuse to goof off instead of work.
GTS		99.	Lying comes easily to me.
S	T	100.	Having close friends is not as important as many people say.
GTS		101.	I can work hard, and for a long time, without feeling tired.
P	T	102.	Sometimes part of my body has seemed smaller than it usually is.
P	T	103.	I sometimes have to touch myself to make sure I'm still there.
S	T	104.	People are usually better off if they stay aloof from emotional involvements with most others.
GTS		105.	I am a cautious person.
GTS		106.	People would describe me as a pretty energetic person.
P	T	107.	Sometimes people whom I know well begin to look like strangers.
I	F	108.	I believe that most light bulbs are powered by electricity.
GTS		109.	Sometimes I will suddenly feel scared for no good reason.
P	T	110.	I sometimes have had the feeling that some parts of my body are not attached to the same person.
S	F	111.	Knowing that I have friends who care about me gives me a sense of security.
P	F	112.	I have never had the passing feeling that my arms or legs have become longer than usual.
GTS		113.	I get a kick out of really scaring people.
GTS		114.	I often get out of things by making up believable excuses.
GTS		115.	I sometimes get too upset by minor setbacks.
S	F	116.	I sometimes become deeply attached to people I spend a lot of time with.
P	T	117.	Parts of my body occasionally seem dead or unreal.
GTS		118.	I would much rather party than work.
GTS		119.	In my life, I would rather try to do too much than too little.

S	T	120.	People sometimes think that I am shy when I really just want to be left alone.
M	T	121.	I have had the momentary feeling that I might not be human.
P	T	122.	Sometimes I have had a passing thought that some part of my body was rotting away.
P	T	123.	My hearing is sometimes so sensitive that ordinary sounds become uncomfortable.
M	T	124.	I have felt that I might cause something to happen just by thinking too much about it.
S	F	125.	Just being with friends can make me feel really good.
S	T	126.	People who try to get to know me better usually give up after awhile.
GTS		127.	I really enjoy beating the system.
I	F	128.	On some mornings, I didn't get out of bed immediately when I first woke up.
S	T	129.	I could be happy living all alone in a cabin in the woods or mountains.
S	F	130.	When I move to a new city, I feel a strong need to make new friends.
GTS		131.	I sometimes rush from one activity to another without pausing for a rest.
S	T	132.	I'm much too independent to really get involved with other people.
S	T	133.	My emotional responses seem very different from those of other people.
S	F	134.	When things are bothering me, I like to talk to other people about it.
S	T	135.	There are few things more tiring than to have a long, personal discussion with someone.
GTS		136.	I often experience strong emotions such as anxiety or anger without really knowing why.
S	T	137.	People often expect me to spend more time talking with them than I would like.
P	T	138.	Often I have a day when indoor lights seem so bright that they bother my eyes.
M	F	139.	I have never doubted that my dreams are the products of my own mind.
GTS		140.	I like to stir up some excitement when things are getting dull.
GTS		141.	I would never hurt other people just to get what I want.
P	T	142.	At times I have wondered if my body was really my own.
I	T	143.	Driving from New York to San Francisco is generally faster than flying between these cities.

GTS		144.	If I had to choose, I would prefer having to sit through a long concert of bad music to being in a bank during an armed robbery.
P	T	145.	Sometimes I have felt that I could not distinguish my body from other objects around me.
GTS		146.	It takes a lot to get me excited.
S	T	147.	I don't really feel very close to my friends.
P	T	148.	Occasionally it has seemed as if my body had taken on the appearance of another person's body.
P	T	149.	I have sometimes had the feeling that my body is decaying inside.
GTS		150.	When I'm having a good time, I don't worry about the consequences.
I	F	151.	There have been times when I have dialed a telephone number only to find that the line was busy.
GTS		152.	I get the most fun out of things that others consider immoral or illegal.
GTS		153.	My mood sometimes changes (for example, from happy to sad, or vice versa) without good reason.
P	T	154.	I have had the momentary feeling that my body has become misshapen.
P	T	155.	I have sometimes felt confused as to whether my body was really my own.
GTS		156.	I lead an active life.
I	T	157.	I find that I often walk with a limp, which is the result of a skydiving accident.
GTS		158.	People sometimes tell me to slow down and "take it easy."
GTS		159.	I have the ability to approach tasks in such a way that they become interesting or fun.
M	T	160.	Things sometimes seem to be in different places when I get home, even though no one has been there.
S	F	161.	If given the choice, I would much rather be with others than be alone.
P	F	162.	The boundaries of my body always seem clear.
M	T	163.	If reincarnation were true, it would explain some unusual experiences I have had.
GTS		164.	I put a lot of energy into everything I do.
GTS		165.	I can get very upset when little things don't go my way.
GTS		166.	I often stop in the middle of one activity to start another one.
S	F	167.	I have often found it hard to resist talking to a good friend, even when I have other things to do.

GTS		168.	I often feel lively and cheerful for no particular reason.
M	T	169.	Horoscopes are right too often for it to be a coincidence.
I	T	170.	I go at least once every two years to visit either northern Scotland or same part of Scandinavia.
GTS		171.	If I had to choose, I would prefer being in a flood to unloading a ton of newspapers from a truck.
P	T	172.	I have sometimes had the feeling that one of my arms or legs is disconnected from the rest of my body.
I	F	173.	There have been a number of occasions when people I know have said hello to me.
GTS		174.	I often worry about things I have done or said.
S	T	175.	I find that people too often assume that their daily activities and opinions will be interesting to me.
GTS		176.	I am often nervous for no reason.
I	F	177.	On some occasions I have noticed that some other people are better dressed than myself.
P	T	178.	For several days at a time I have had such a heightened awareness of sights and sounds that I cannot shut them out.
M	T	179.	The hand motions that strangers make seem to influence me at times.
I	T	180.	I have never combed my hair before going out in the morning.
GTS		181.	I don't ever like to stay in one place for long.
GTS		182.	In my life, interesting and exciting things happen every day.
M	T	183.	I have had the momentary feeling that someone's place has been taken by a look-alike.
M	T	184.	I have noticed sounds on my records that are not there at other times.
M	F	185.	It is not possible to harm others merely by thinking bad thoughts about them.
P	T	186.	I have had the momentary feeling that the things I touch remain attached to my body.
S	T	187.	I attach very little importance to having close friends.
S	T	188.	Playing with children is a real chore.
GTS		189.	I am often troubled by guilt feelings.
GTS		190.	I am usually enthusiastic about the things that I do.
GTS		191.	I have more energy than most people I know.

P	T	192.	Sometimes when I look at things like tables and chairs, they seem strange.
M	T	193.	The government refuses to tell us the truth about flying saucers.
P	T	194.	Sometimes I have had the feeling that a part of my body is larger than it usually is.
GTS		195.	I've done a lot of things for which I could have been (or was) arrested.
I	T	196.	I cannot remember a time when I talked with someone who wore glasses.
M	T	197.	I have occasionally had the silly feeling that a TV or radio broadcaster knew I was listening to him.
GTS		198.	Before I make a decision I usually try to consider all sides of the issue.
GTS		199.	I get excited when I think about the future.
GTS		200.	I often take my anger out on those around me.
GTS		201.	Most days I have a lot of "pep" and vigor.
S	F	202.	I have always enjoyed looking at photographs of friends.
GTS		203.	I like to show-off.
GTS		204.	I rely on careful reasoning when making up my mind.
S	F	205.	It's fun to sing with other people.
P	T	206.	I have felt that something outside my body was a part of my body.
M	T	207.	At times I perform certain little rituals to ward off negative influences.
P	T	208.	Ordinary colors sometimes seem much too bright to me.

Questions about obstetric complications asked during interview with biological mothers:

Did you have any of these complications during your pregnancy or delivery?

1. Rubella (German Measles) or Syphillis:

2. Rhesus incompatibility (Rh incompatibility):

   Antigens called Rh factors may or may not be present in an individual's red blood cells (so you can be Rh positive or Rh negative). If the mother is Rh negative and the fetus is Rh positive, you have Rh incompatibility, and it may cause problems for the fetus (blood clumping, anemia, jaundice). Usually tested for with amniocentesis and can be treated.

3. Pre-eclampsia that was severe and/or lead to early induction or hospitalization

   Pre-eclampsia and eclampsia are forms of high blood pressure that occur during pregnancy and are accompanied by protein in the urine and edema (swelling). As the names suggest, these two disorders are related. Pre-eclampsia, sometimes called toxemia of pregnancy, may develop into the more severe eclampsia, which is pre-eclampsia together with seizure. These conditions usually develop during the second half of pregnancy (after 20 weeks), though sometimes they develop shortly after birth, and, in very rare situations, they occur before 20 weeks of pregnancy. Usually treated with bedrest and blood pressure meds.

4. APH or threatened abortion:

   This is the presumed diagnosis when any bloody vaginal discharge or vaginal bleeding occurs in the first half of pregnancy.

5. Premature rupture of membranes
   - How early did they rupture?

6. Labor of >36 or <3 hrs
   - How long?
   - If not: how long was your labor?

7. Twin/multiple birth, complicated
   - How was it complicated?

8. Cord prolapse
   This is when the umbilical cord comes out ahead of the baby at delivery.
   - If not prolapsed: was the cord around the baby's neck, or was it knotted?

9. Gestational age <37 wks or >42 wks
   - If not: was the baby "premature" or "postmature"? How many weeks?

10. Caesarian, complicated or emergency
    - What happened? How was it complicated?
11. Breech or abnormal presentation
    Breech is when the baby is upside down (butt first or feet first). Reversed is facing out instead of towards the mother's spine.

12. High or "difficult" forceps
    High forceps are when the baby isn't descended low enough to just need help at the end, and has to be pulled out from higher up the birth canal.
    - If not: were forceps or other instrumental delivery used? Why?

13. Birthweight < 4.5 lbs
    - If not: was the baby <5.5 lbs or "small"?

14. Incubator >4 wks
    - If not: was the baby put into an incubator at all? Why? For how long?
    - Was the baby born "blue"?
    - Did the baby need resuscitation? Why?

15. Did the baby have any physical abnormalities at birth? Describe.
Like webbed toes, facial abnormalities, or ANYTHING. Note if these were corrected with surgery (since then we may not notice them on the kid).

16. Did you drink alcohol during your pregnancy? How much?

17. Did you smoke cigarettes during your pregnancy? How much?

18. Did you use drugs during your pregnancy? How much?

Waldrop Scale for assessing minor physical anomalies

HEAD

1. Head circumference

Pull tape firmly over globella (frown marks) and supra-orbital ridges (enlarged ridges above eyes) in the front, and around the part of the back that gives maximum circumference

Score = 1: >59.8 cm. (men) or >56.9 cm. (women)
Score = 2: >61.4 cm. (men) or >58.2 cm. (women)

EYES

2. Epicanthus of eyes

This is the fold of skin that may partly cover the lacrimal caruncle (the little round bit on the inner edge of the eye). With the subject looking straight ahead, look for a vertical skin fold that covers the lacrimal caruncle (may be on both OR one eye)

Score = 1: partial coverage
Score = 2: total coverage

3. Hypertelorism (wide-spaced eyes)

Hold a clear plastic ruler across the bridge of the nose, using the inside corners of the eyes as reference points. Measure (in cm) from the edge of each inner eye.

Score = 1: >3.2 cm. (men and women)
Score = 2: >3.5 cm. (men and women)

EARS

4. Low-seated ears

Hold a pencil (Or other straight object) next to the side of the head, and line up the end of the pencil with the bridge of the nose and the outer corner of the eye. Make the pencil horizontal to the ground. Observe where the ear is compared to the line of the pencil.

Score = 1: no more than ¼ of the ear is above the pencil
Score = 2: the entire ear is below the pencil

5. Adherent ear lobes

Look at where the lobe of the ear is at the lowest point of attachment to the neck. Also, look at the angle of the lower edge of the ear.

Score = 1: there is no lobe dangling below the point of attachment to the head AND the lower edge of the ear is horizontal to the floor (points straight back to the back of the neck)

Score = 2: there is no lobe dangling below the point of attachment to the head AND the lower edge of the ear is angled towards the crown of the head.

6. Malformed ears

Look for gross malformations of the ear (these are very rare)

Score = 1: grossly malformed ears

7. Asymmetrical ears

Look for ears that are obviously different from each other by visual inspection. Differences may be in size, in degree of protrusion from head vs. lying flat, the shape, etc. If one ear is low seated (item 5), this is counted as a asymmetry as well on this item.

Score = 1: one or more asymmetries

8. Soft and pliable ears

Palpate the ears between thumb and first finger.

Score = 1: soft and pliable ears that do not spring back into place (compared to ears with strong cartilage)

MOUTH

9. High-steepled palate

Look at the shape of the roof of the mouth. A cross section of a normally shaped mouth would give a smooth, rounded dome.

Score = 1: the roof has a narrow flat area across the top
Score = 2: the roof is an acute angle rather than an arch

10. Furrowed tongue

Look for deep furrows on the tongue. A normal tongue has only up to one deep furrow along the center line.

Score = 1: one or more deep furrows not along the center line of the tongue

11. Tongue with smooth-rough spots

Look for localized thickening of the surface of the tongue (rough spots). Make sure this is not due to elevated papillae caused by recent consumption of certain foods (e.g., sour patch kids). This condition is extremely rare

Score = 1: presence of smooth and rough spots

HANDS

12. Curved fifth finger

Look for the fifth finger to curve inward towards the other fingers.

Score = 1: small degree of curvature
Score = 2: large degree of curvature

13. Single transverse palmar crease

Look for a single, unbroken line in the palm of the hand going more or less straight across the hand (normally have two lines that may not go all the way to the edge of the palm)

Score = 1: single transverse crease present

FEET

14. Third toe larger than the second

Have subject stand with weight distributed evenly on both feet and toes held in an extended position.

Score = 1: second and third toes are same length
Score = 2: third toe is obviously longer than second

15. Partial syndactylia (webbing) of two middle toes

Look at second and third toes. Everyone has some webbing, but examine how far the webbing does, and how many indentations there are at the base of the toes (normally there are four).

Score = 1: webbing extends to near the lower toe joints AND there are only three indentations at the base of the toes

16. Big gap between first and second toes

Look at the space between the big and second toes. A gap must have a flat space between the toes.

Score = 1: there is a flat base across the gap between the big and second toes that is more than half the width of the second toe

GLOSSARY OF ABBREVIATIONS

AB ridge count: The AB ridge count is the number of ridges falling between an imaginary line from the a and b triradii (the triangular convergence of lines at the base of the index and middle fingers). The AB ridge count is a measure of fluctuating asymmetry (FA).

ATD angle: The ATD angle is the angle formed by connecting the a and d triradii (the triangular convergence of lines at the base of the index and pinkie fingers) and the t triradii (the triangular convergence of lines at near the base of the palm). The ATD angle is a measure of fluctuating asymmetry (FA).

DA: Directional asymmetry. DA refers to deviation in either direction from a naturally-occurring asymmetry (e.g., deviation from moderate right-handedness resulting in either left-handedness, ambidexterity or extreme right-handedness). DA is thought to reflect an individual's degree of developmental instability.

DI: Developmental instability. DI refers to the inability of an individual to buffer the effects of environmental stressors (e.g., obstetric complications) on development and express his/her genotype precisely.

FA: Fluctuating asymmetry. FA is the degree to which an individual varies on certain traits (e.g., eye height, dermatoglyphic patterns) that are symmetric at the genotypic and population level. High FA is thought to reflect an individual's degree of developmental instability.

MIS: The Magical Ideation Scale (Eckblad & Chapman, 1983). The MIS is a paper and pencil measure of schizotyp that assesses magical ideation (usual beliefs).

MPAs: Minor physical anomalies. MPAs are abnormalities in physical features particularly affected by disruptions in fetal growth rate (e.g., ear height; eye spacing). A higher rate of MPAs is thought to reflect an individual's degree of developmental instability.

PAS: The Perceptual Aberration Scale (Chapman, Chapman & Raulin, 1978). The PAS is a paper and pencil measure of schizotypy that assesses perceptual aberrations (unusual perceptual and sensory experiences)

RSAS: The Revised Social Anhedonia Scale (Eckblad, Chapman, Chapman & Mishlove, 1982). The RSAS is a pencil and paper measure of schizotypy that assesses social anhedonia (lack of pleasure in social interactions).

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